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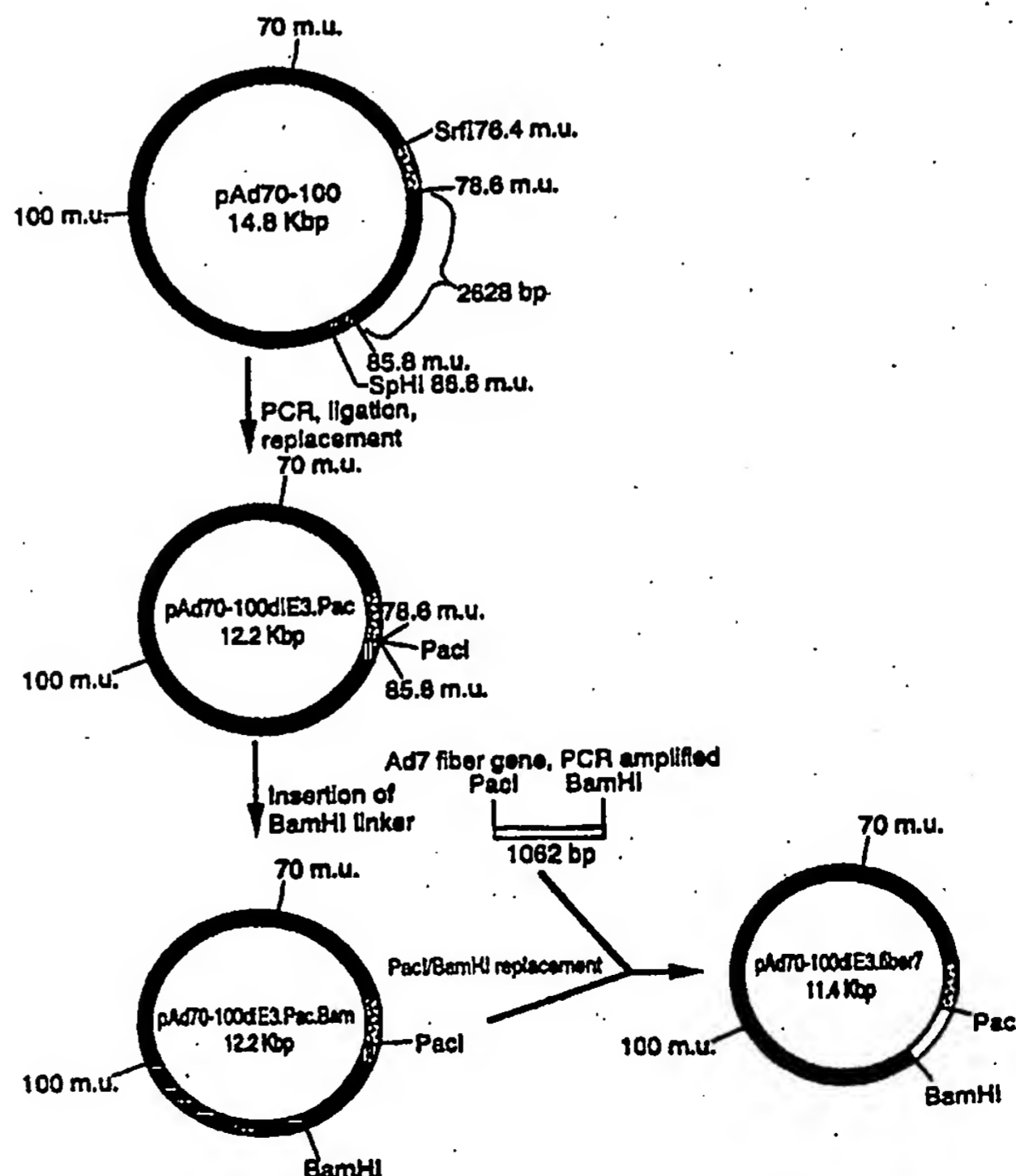
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(71) Applicants (for all designated States except US): CORNELL RESEARCH FOUNDATION, INC. [US/US]; Cornell Business & Technology Park, Suite 105, 20 Thornwood Drive, Ithaca, NY 14850 (US). GENVEC, INC. [US/US]; 12111 Parklawn Drive, Rockville, MD 20852 (US).			(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).
(72) Inventors; and (75) Inventors/Applicants (for US only): CRYSTAL, Ronald, G. [US/US]; 13712 Canal Vista Court, Potomac, MD 20854 (US). FALCK-PEDERSEN, Erik [US/US]; 8714 Buena Vista Drive, Dobbs Ferry, NY 10522 (US). GALL, Jason [US/US]; 420 E. 70th Street #10F, New York, NY 10021 (US). KOVESDI, Imre [CA/US]; 7713 Warbler			
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(54) Title: CHIMERIC ADENOVIRAL COAT PROTEIN AND METHODS OF USING SAME

(57) Abstract

The present invention provides a chimeric adenoviral coat protein (particularly a chimeric adenovirus hexon protein). The chimeric adenovirus coat protein has a decreased ability or inability to be recognized by a neutralizing antibody directed against the corresponding wild-type adenovirus coat protein.



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## CHIMERIC ADENOVIRAL COAT PROTEIN AND METHODS OF USING SAME

### TECHNICAL FIELD OF THE INVENTION

The present invention relates to a chimeric adenoviral coat protein and a recombinant adenovirus comprising same. In particular, the invention provides a chimeric adenoviral hexon protein and a recombinant adenovirus comprising the chimeric adenoviral hexon protein. Such a recombinant adenovirus can be employed *inter alia* in gene therapy.

### BACKGROUND OF THE INVENTION

*In vivo* gene therapy is a strategy in which nucleic acid, usually in the form of DNA, is administered to modify the genetic repertoire of target cells for therapeutic purposes. This can be accomplished efficiently using a recombinant adenoviral vector encoding a so-called "therapeutic gene". A therapeutic gene is generally considered a gene that corrects or compensates for an underlying protein deficit or, alternately, a gene that is capable of down-regulating a particular gene, or counteracting the negative effects of its encoded product, in a given disease state or syndrome. Recombinant adenoviral vectors have been used to transfer one or more recombinant genes to diseased cells or tissues in need of treatment. As reviewed by Crystal, Science, 270, 404-410 (1995), such vectors are preferred over other vectors commonly employed for gene therapy (e.g., retroviral vectors) since adenoviral vectors can be produced in high titers (i.e., up to  $10^{13}$  viral particles/ml), and they efficiently transfer genes to nonreplicating, as well as replicating, cells. Moreover, adenoviral vectors are additionally preferred based on their normal tropism for

the respiratory epithelium in cases where the targeted tissue for somatic gene therapy is the lung, as well as for other reasons (see, e.g., Straus, In Adenoviruses, Plenan Press, New York, NY, 451-496 (1984)); Horwitz et al., In Virology, 2nd Ed., Fields et al., eds., Raven Press, New York, NY, 1679-1721 (1990); Berkner, BioTechniques, 6, 616 (1988); Chanock et al., JAMA, 195, 151 (1966); Haj-Ahmad et al., J. Virol., 57, 267 (1986); and Ballay et al., EMBO, 4, 3861 (1985)).

There are 49 human adenoviral serotypes, categorized into 6 subgenera (A through F) based on nucleic acid comparisons, fiber protein characteristics, and biological properties (Crawford-Miksza et al., J. Virol., 70, 1836-1844 (1996)). The group C viruses (e.g., serotypes 2 and 5, or Ad2 and Ad5) are well characterized. It is these serotypes that currently are employed for gene transfer studies, including human gene therapy trials (see, e.g., Rosenfeld et al., Science, 252, 431-434 (1991); Rosenfeld et al., Cell, 68, 143-155 (1992); Zabner, Cell, 75, 207-216 (1993); Crystal et al., Nat. Gen., 8, 42-51 (1994); Yei et al., Gene Therapy, 1, 192-200 (1994); Chen et al., Proc. Natl. Acad. Sci., 91, 3054-3057 (1994); Yang et al., Nat. Gen., 7, 362-369 (1994); Zabner et al., Nat. Gen., 6, 75-83 (1994)). Other groups and serotypes include, but are not limited to: group A (e.g., serotypes 12 and 31), group B (e.g., serotypes 3 and 7), group D (e.g., serotypes 8 and 30), group E (e.g., serotype 4) and group F (e.g., serotypes 40 and 41) (Horwitz et al., supra).

In terms of general structure, all adenoviruses examined to date are nonenveloped, regular icosahedrons of about 65 to 80 nanometers in diameter. Adenoviruses are comprised of linear, double-stranded DNA that is complexed with core proteins and surrounded by the adenoviral capsid. The capsid is comprised of 252 capsomeres, of which 240 are hexons and 12 are pentons. The hexon

capsomere provides structure and form to the capsid (Pettersson, in The Adenoviruses, pp. 205-270, Ginsberg, ed., (Plenum Press, New York, NY, 1984)), and is a homotrimer of the hexon protein (Roberts et al., Science, 232, 1148-1151 (1986)). The penton comprises a penton base, which is bound to other hexon capsomeres, and a fiber, which is noncovalently bound to, and projects from, the penton base. The penton fiber protein comprises three identical polypeptides (i.e., polypeptide IV). The Ad2 penton base protein comprises five identical polypeptides (i.e., polypeptide III) of 571 amino acids each (Boudin et al., Virology, 92, 125-138 (1979)).

The adenoviruses provide an elegant and efficient means of transferring therapeutic genes into cells. However, one problem encountered with the use of adenoviral vectors for gene transfer *in vivo* is the generation of antibodies to antigenic epitopes on adenoviral capsid proteins. If sufficient in titer, the antibodies can limit the ability of the vector to be used more than once as an effective gene transfer vehicle. For instance, animal studies demonstrate that intravenous or local administration (e.g., to the lung, heart or peritoneum) of an adenoviral type 2 or 5 gene transfer vector can result in the production of antibodies directed against the vector which prevent expression from the same serotype vector administered 1 to 2 weeks later (see, e.g., Yei et al., supra; Zabner (1994), supra; Setoguchi et al., Am. J. Respir. Cell. Mol. Biol., 10, 369-377 (1994); Kass-Eisler et al., Gene Therapy, 1, 395-402 (1994); Kass-Eisler et al., Gene Therapy 3, 154-162 (1996)). This is a drawback in adenoviral-mediated gene therapy, since many uses of an adenoviral vector (e.g., for prolonged gene therapy) require repeat administration inasmuch as the vector does not stably integrate into the host cell genome. The mechanism by which antibodies

directed against an adenovirus are able to prevent or reduce expression of an adenoviral-encoded gene is unclear. However, the phenomenon is loosely referred to as "neutralization", and the responsible antibodies are termed "neutralizing antibodies."

There are three capsid structures against which neutralizing antibodies potentially can be elicited: fiber, penton, and hexon (Pettersson, supra). The hexon protein, and to a lesser extent the fiber protein, comprise the main antigenic determinants of the virus, and also determine the serotype specificity of the virus (Watson et al., J. Gen. Virol., 69, 525-535 (1988); Wolfort et al., J. Virol., 62, 2321-2328 (1988); Wolfort et al., J. Virol., 56, 896-903 (1985); Crawford-Miksza et al., supra). Researchers have examined and compared the structure of these coat proteins of different adenoviral serotypes in an effort to define the regions of the proteins against which neutralizing antibodies are elicited.

The Ad2 hexon trimer is comprised of a pseudo-hexagonal base and a triangular top formed of three towers (Roberts et al., supra; Athappilly et al., J. Mol. Biol., 242, 430-455 (1994)). The base pedestal consists of two tightly packed eight-stranded antiparallel beta barrels stabilized by an internal loop. The predominant regions in hexon protein against which neutralizing antibodies are directed appear to be in loops 1 and 2 (i.e., LI or 11, and LII or 12, respectively) in one of the three towers. For instance, Kinloch et al. (J. Biol. Chem., 258, 6431-6436 (1984)) compared adenoviral hexon sequences and theorized that the serotype-specific antigenic determinants on hexon are located in amino acid residues 120 to 470 encompassing the 11 and 12 loops since type-specific sequence differences are mainly concentrated in this region. Toogood et al. (J. Gen.

Virol., 73, 1429-1435 (1992)) used peptides from this region to generate specific anti-loop antisera and confirmed that antibodies against residues 281-292 of 11 and against residues 441-455 of 12 were sufficient to neutralize infection. Also, Crompton et al. (J. Gen. Virol., 75, 133-139 (1994)) modified these loops to accept neutralizing epitopes from polio virus, and demonstrated that infection with the resultant adenoviral vector generated neutralizing immunity against polio virus. More recently it was demonstrated that the hexon protein is composed of seven discrete hypervariable regions in loops and 1 and 2 (HVR1 to HVR7) which vary in length and sequence between adenoviral serotypes (Crawford-Miksza et al., supra).

Less is known regarding the regions of the fiber protein against which neutralizing antibodies potentially can be directed. However, much data is available on the structure of the fiber protein. The trimeric fiber protein consists of a tail, a shaft, and a knob (Devaux et al., J. Molec. Biol., 215, 567-588 (1990)). The fiber shaft region is comprised of repeating 15 amino acid motifs, which are believed to form two alternating beta strands and beta bends (Green et al., EMBO J., 2, 1357-1365 (1983)). The overall length of the fiber shaft region and the number of 15 amino acid repeats differ between adenoviral serotypes. The receptor binding domain of the fiber protein and sequences necessary for fiber trimerization are localized in the knob region encoded by roughly the last 200 amino acids of the protein (Henry et al., J. Virol., 68(8), 5239-5246 (1994)); Xia et al., Structure, 2(12), 1259-1270 (1994)). Furthermore, all adenovirus serotypes appear to possess a type of specific moiety located in the knob region (Toogood et al., supra.)

Given the existence of these potential epitopes in hexon protein and fiber protein, it is understandable

that, in some cases, difficulties have been encountered using adenovirus as a vector for gene therapy. Accordingly, recombinant adenoviral vectors capable of escaping such neutralizing antibodies (in the event they are preexisting and hamper gene expression commanded by adenovirus in an initial dose), and which would allow repeat doses of adenoviral vectors to be administered, would significantly advance current gene therapy methodology.

Thus, the present invention seeks to overcome at least some of the aforesaid problems of recombinant adenoviral gene therapy. In particular, it is an object of the present invention to provide a recombinant adenovirus comprising a chimeric coat protein that has a decreased ability or inability to be recognized by antibodies (i.e., neutralizing antibodies) directed against the corresponding wild-type adenovirus coat protein. These and other objects and advantages of the present invention, as well as additional inventive features, will be apparent from the description of the invention provided herein.

#### **BRIEF SUMMARY OF THE INVENTION**

The present invention provides a chimeric adenovirus coat protein (particularly a chimeric adenovirus hexon protein) comprising a nonnative amino acid sequence. The chimeric adenovirus coat protein is not recognized by, or has a decreased ability to be recognized by, a neutralizing antibody directed against the corresponding wild-type (i.e., native) coat protein. The chimeric adenovirus coat protein enables a vector (such as an adenovirus) comprising the corresponding protein to be administered repetitively, or to be administered following administration of an adenovirus vector comprising the corresponding wild-type coat protein. It also enables a

vector (such as an adenovirus) comprising the chimeric protein to be administered and effect gene expression in the case where there are preexisting neutralizing antibodies directed against the wild-type adenovirus coat protein. The present invention also provides a vector, particularly an adenoviral vector, that comprises a chimeric adenovirus coat protein such as chimeric adenovirus hexon protein (and which optionally further comprises a chimeric adenovirus fiber and/or penton base protein), and methods of constructing and using such a vector.

#### BRIEF DESCRIPTION OF THE FIGURES

**Figure 1** is a diagram of the method employed to construct the vector pAd70-100dlE3.fiber7.

**Figure 2** is a partial restriction map of the vector pGBS.59-100(HSF:RGD).

#### DETAILED DESCRIPTION OF THE INVENTION

The present invention provides, among other things, a chimeric adenovirus coat protein. The chimeric adenovirus coat protein comprises a nonnative amino acid sequence, such that the chimeric adenovirus coat protein (or a vector comprising the chimeric adenovirus coat protein) has a decreased ability or inability to be recognized by antibodies (e.g., neutralizing antibodies) directed against the corresponding wild-type adenovirus coat protein.

#### Chimeric Adenovirus Coat Protein

A "coat protein" according to the invention is either an adenoviral penton base protein, an adenoviral hexon protein, or an adenoviral fiber protein. Preferably a coat protein is a adenoviral hexon protein or an adenoviral fiber protein. Any one of the serotypes of

human or nonhuman adenovirus can be used as the source of the coat protein, or its gene or coding sequence. Optimally, however, the adenovirus coat protein is that of a Group B or C adenovirus and, preferably, is that of Ad1, Ad2, Ad3, Ad5, Ad6, Ad7, Ad11, Ad12, Ad14, Ad16, Ad21, Ad34, Ad35, Ad40, Ad41, or Ad48.

The chimeric adenovirus coat protein (or a vector, such as adenoviral vector, comprising the chimeric adenovirus coat protein) has a decreased ability or an inability to be recognized by an antibody (e.g., a neutralizing antibody) directed against the corresponding wild-type adenovirus coat protein. A "neutralizing antibody" is an antibody that either is purified from or is present in serum. As used herein, an antibody can be a single antibody or a plurality of antibodies. An antibody is "neutralizing" if it inhibits infectivity of (i.e., cell entry) or gene expression commanded by an adenovirus comprising wild-type coat protein, or if it exerts a substantial deleterious effect on infectivity of or gene expression commanded by an adenovirus comprising wild-type coat protein, as compared, for instance, to any effect on any other adenoviral property.

An ability or inability of a chimeric coat protein to "be recognized by" (i.e., interact with) a neutralizing antibody directed against the wild-type adenovirus coat protein can be assessed by a variety of means known to those skilled in the art. For instance, the removal of one or more epitopes for a neutralizing antibody present in a wild-type adenovirus coat protein to generate a chimeric adenovirus coat protein will result in a decreased ability or inability of the chimeric coat protein to be recognized by the neutralizing antibody. Also, such a decreased ability or inability to interact with a neutralizing antibody directed against wild-type coat protein can be demonstrated by means of a

neutralization test (see, e.g., Toogood et al., supra; Crawford-Miksza et al., supra; Mastrangeli et al., Human Gene Therapy, 7, 79-87 (1996)), or as further described herein.

Generally, an "inability" of a chimeric adenovirus coat protein (or a vector comprising a chimeric adenovirus coat protein) to be recognized by a neutralizing antibody directed against wild-type adenovirus coat protein means that such an antibody does not interact with the chimeric coat protein, and/or exhibits no substantial deleterious effect on infectivity of or gene expression commanded by an adenovirus comprising wild-type coat protein, as compared, for instance, to any effect on any other adenoviral property.

A "decreased ability" to be recognized by neutralizing antibody directed against wild-type adenovirus coat protein refers to any decrease in the ability of the chimeric adenovirus coat protein (or a vector comprising the chimeric coat protein) to be recognized by an antibody directed against the corresponding wild-type adenovirus coat protein as compared to the wild-type adenovirus coat protein. When such ability/inability is assessed by means of a neutralization test in particular, preferably a "decreased ability" to be recognized by a neutralizing antibody directed against wild-type adenovirus coat protein is exhibited by from about a 10% to about a 99% increase in the ability of a recombinant adenovirus comprising the chimeric coat protein to cause a visible cytopathic effect (c.p.e.) in cells such as A549 cells or COS-1 cells (or other such cells appropriate for a neutralization assay) in the presence of the neutralizing antibody as compared to an adenovirus comprising the wild-type coat protein against which the neutralizing antibody is directed.

Furthermore, a decreased ability or inability of an adenovirus chimeric coat protein (or a vector comprising a chimeric adenovirus coat protein) to interact with a neutralizing antibody can be shown by a reduction of inhibition (from about 10% to about 99%) or no inhibition at all of cell infectivity by a recombinant vector (such as an adenoviral vector) containing the chimeric coat protein as compared to a recombinant vector containing the wild-type protein. Also, a decreased ability or inability of an adenovirus chimeric coat protein (or a vector comprising a chimeric adenovirus coat protein) to interact with a neutralizing antibody can be shown by a reduction of inhibition (from about 10% to about 99%) or no inhibition at all of gene expression commanded by a recombinant vector (such as an adenoviral vector) containing the chimeric coat protein as compared to a recombinant vector containing the wild-type coat protein. These tests can be carried out when the recombinant adenovirus containing the chimeric coat protein is administered following the administration of an adenovirus containing the wild-type coat protein, or when the recombinant adenovirus is administered to a host that has never before encountered or internalized adenovirus (i.e., a "naïve" host). These methods are described, for instance, in the Examples which follow as well as in Mastrangeli et al., supra. Other means such as are known to those skilled in the art also can be employed.

The coat protein is "chimeric" in that it comprises a sequence of amino acid residues that is not typically found in the protein as isolated from, or identified in, wild-type adenovirus, which comprises the so-called native coat protein, or "wild-type coat protein". The chimeric coat protein thus comprises (or has) a "nonnative amino acid sequence". By "nonnative amino acid sequence" is meant any amino acid sequence (i.e., either component

residues or order thereof) that is not found in the native coat protein of a given serotype of adenovirus, and which preferably is introduced into the coat protein at the level of gene expression (i.e., by production of a nucleic acid sequence that encodes the nonnative amino acid sequence). Generally, the nonnative amino acid sequence can be obtained by deleting a portion of the amino acid sequence, deleting a portion of the amino acid sequence and replacing the deleted amino sequence with a so-called "spacer region", or introducing the spacer region into an unmodified coat protein. Preferably such manipulations result in a chimeric adenovirus coat protein according to the invention that is capable of carrying out the functions of the corresponding wild-type adenovirus coat protein (or, at least that when incorporated into an adenovirus, will allow appropriate virion formation and will not preclude adenoviral-mediated cell entry); and, optimally, that is not impeded in its proper folding. Also, it is desirable that the manipulations do not result in the creation of new epitopes for differing antibodies, unless, of course, such epitopes do not interfere with use of an adenovirus containing the chimeric coat protein as a gene transfer vehicle *in vivo*.

In particular, a nonnative amino acid sequence according to the invention preferably comprises a deletion of a region of a wild-type adenovirus coat protein, particularly an adenovirus hexon or fiber protein. Optimally the resultant nonnative amino acid sequence is such that one or more of the existing epitopes for neutralizing antibodies directed against the corresponding wild-type adenovirus coat protein have been rendered non-immunogenic. Desirably, the region deleted comprises from about 1 to about 750 amino acids, preferably from about 1 to about 500 amino acids, and optimally from about 1 to about 300 amino acids. It also is desirable that the

region deleted comprises a smaller region less than about 200 amino acids, preferably less than about 100 amino acids, and optimally less than about 50 amino acids. The chimeric coat protein also desirably comprises a plurality of such deletions. Thus, according to the invention, the chimeric adenovirus coat protein comprises modification of one or more amino acids, and such modification is made in one or more regions.

In a preferred embodiment of the present invention, a nonnative amino acid sequence comprises a deletion of one or more regions of a wild-type adenovirus hexon protein, wherein preferably the hexon protein is the Ad2 hexon protein [SEQ ID NO:2] (which is encoded by the sequence of SEQ ID NO:1; GenBank® Data Bank Accession Number U20821), or the Ad5 hexon protein [SEQ ID NO:3] (GenBank® Data Bank Accession Number M73260, which is encoded by the sequence of SEQ ID NO:4), or the Ad7 hexon protein (GenBank® Data Bank Accession Number x76551). Alternately, preferably the hexon protein is the protein sequence reported by Crawford-Miksza et al. (Ad2 hexon [SEQ ID NO:52], Ad5 hexon [SEQ ID NO:54]). In particular, the sequences of Crawford-Miksza et al. differ over those reported in the GenBank® Data Bank in that the amino acid residue reported as the first in the Crawford-Miksza et al. sequences is not Met, and the Ad5 hexon sequence is reported as terminating with "Gln His" instead of with "Thr Thr". As employed herein, the numbering of adenovirus hexon amino acid residues corresponds to that in Crawford-Miksza et al.

Desirably the region(s) of the deletion comprises an internal hexon protein sequence ("internal" meaning not at or near the C- or N-terminus of the protein; "near" referring to a distance of 500 amino acids or less ), preferably a hypervariable region, e.g., as reported in Crawford-Miksza et al. In particular, optimally, the

internal region of the wild-type hexon protein that is deleted to generate the chimeric hexon protein comprises the entirety of 11 loop, preferably from about residue 131 to about residue 331 of the Ad2 hexon protein [SEQ ID NO:6] (which is encoded by the sequence of SEQ ID NO:5), or the corresponding region from another adenoviral serotype, e.g., particularly the corresponding region from Ad1, Ad5 [SEQ ID NO:8] (which is encoded by the sequence of SEQ ID NO:7), Ad6, Ad7, Ad8, Ad12, Ad16, Ad40, Ad41, Ad48, BAV3, or MAV1, especially as reported in Crawford-Miksza et al., supra.

Alternately, preferably the internal region of the wild-type hexon protein that is deleted to produce the chimeric hexon protein comprises one or more regions (e.g., smaller regions) of the 11 loop. Optimally the region deleted comprises a hypervariable region. Desirably the one or more regions of the 11 loop deleted are regions (i.e., hypervariable regions) selected from this group consisting of the HVR1 region, the HVR2 region, the HVR3 region, the HVR4 region, the HVR5 region, and the HVR6 region. Moreover, preferably the region of the wild-type protein that is deleted (or otherwise manipulated as described herein) occurs on the external surface of the hexon protein. Thus, HVR2, HVR3, HVR4, and HVR5 -- each of which are externally located regions of the hexon protein -- are particularly preferred for deletion or modification.

The "HVR1 region" preferably comprises from about amino acid 137 to about amino acid 188 of the Ad2 hexon protein [SEQ ID NO:10] (which is encoded by the sequence of SEQ ID NO:9), or the corresponding region from another adenoviral serotype, e.g., particularly the corresponding region from Ad1, Ad3, Ad5 [SEQ ID NO:12] (which is encoded by the sequence of SEQ ID NO:11), Ad6, Ad7, Ad8, Ad11, Ad12, Ad14, Ad16, Ad21, Ad34, Ad35, Ad40, Ad41, Ad48,

BAV3, or MAV1, especially as reported in Crawford-Miksza et al., supra.

The "HVR2 region" preferably comprises from about amino acid 194 to about amino acid 204 of the Ad2 hexon protein [SEQ ID NO:14] (which is encoded by the sequence of SEQ ID NO:13), or the corresponding region from another adenoviral serotype, e.g., particularly the corresponding region from Ad1, Ad3, Ad5 [SEQ ID NO:16] (which is encoded by the sequence of SEQ ID NO:15), Ad6, Ad7, Ad8, Ad11, Ad12, Ad14, Ad16, Ad21, Ad34, Ad35, Ad40, Ad41, Ad48, BAV3, or MAV1, especially as reported in Crawford-Miksza et al., supra.

The "HVR3 region" preferably comprises from about amino acid 222 to about amino acid 229 of the Ad2 hexon protein [SEQ ID NO:18] (which is encoded by the sequence of SEQ ID NO:17), or the corresponding region from another adenoviral serotype, e.g., particularly the corresponding region from Ad1, Ad3, Ad5 [SEQ ID NO:20] (which is encoded by the sequence of SEQ ID NO:19), Ad6, Ad7, Ad8, Ad11, Ad12, Ad14, Ad16, Ad21, Ad34, Ad35, Ad40, Ad41, Ad48, BAV3, or MAV1, especially as reported in Crawford-Miksza et al., supra.

The "HVR4 region" preferably comprises from about amino acid 258 to about amino acid 271 of the Ad2 hexon protein [SEQ ID NO:22] (which is encoded by the sequence of SEQ ID NO:21), or the corresponding region from another adenoviral serotype, e.g., particularly the corresponding region from Ad1, Ad3, Ad5 [SEQ ID NO:24] (which is encoded by the sequence of SEQ ID NO:23), Ad6, Ad7, Ad8, Ad11, Ad12, Ad14, Ad16, Ad21, Ad34, Ad35, Ad40, Ad41, Ad48, BAV3, or MAV1, especially as reported in Crawford-Miksza et al., supra.

The "HVR5 region" preferably comprises from about amino acid 278 to about amino acid 294 of the Ad2 hexon protein [SEQ ID NO:26] (which is encoded by the sequence

of SEQ ID NO:25), or the corresponding region from another adenoviral serotype, e.g., particularly the corresponding region from Ad1, Ad3, Ad5 [SEQ ID NO:28] (which is encoded by the sequence of SEQ ID NO:27), Ad6, Ad7, Ad8, Ad11, Ad12, Ad14, Ad16, Ad21, Ad34, Ad35, Ad40, Ad41, Ad48, BAV3, or MAV1, especially as reported in Crawford-Miksza et al., supra. In particular, preferably the deleted region comprises from about amino acid 297 to about amino acid 304 just outside of the HVR5 region of the Ad2 hexon protein [SEQ ID NO:30] (which is encoded by the sequence of SEQ ID NO:29), or the corresponding region from another adenoviral serotype, e.g., particularly the corresponding region from Ad1, Ad3, Ad5 [SEQ ID NO:32] (which is encoded by the sequence of SEQ ID NO:31), Ad6, Ad7, Ad8, Ad11, Ad12, Ad14, Ad16, Ad21, Ad34, Ad35, Ad40, Ad41, Ad48, BAV3, or MAV1, especially as reported in Crawford-Miksza et al., supra.

The "HVR6 region" preferably comprises from about amino acid 316 to about amino acid 327 of the Ad2 hexon protein [SEQ ID NO:34] (which is encoded by the sequence of SEQ ID NO:33), or the corresponding region from another adenoviral serotype, e.g., particularly the corresponding region from Ad1, Ad3, Ad5 [SEQ ID NO:36] (which is encoded by the sequence of SEQ ID NO:35), Ad6, Ad7, Ad8, Ad11, Ad12, Ad14, Ad16, Ad21, Ad34, Ad35, Ad40, Ad41, Ad48, BAV3, or MAV1, especially as reported in Crawford-Miksza et al., supra.

In another preferred embodiment of the invention, the internal region of the wild-type hexon protein that is deleted to generate the chimeric hexon protein comprises the entirety of the 12 loop, preferably from about residue 423 to about residue 477 of the Ad2 hexon protein [SEQ ID NO:38] (which is encoded by the sequence of SEQ ID NO:37), or the corresponding region from another adenoviral serotype, e.g., particularly the corresponding region from

Ad1, Ad3, Ad5 [SEQ ID NO:40] (which is encoded by the sequence of SEQ ID NO:39), Ad6, Ad7, Ad8, Ad11, Ad12, Ad14, Ad16, Ad21, Ad34, Ad35, Ad40, Ad41, Ad48, BAV3, or MAV1, especially as reported in Crawford-Mikszsa et al., supra. Alternately, preferably the internal region of the wild-type hexon protein that is deleted to produce the chimeric hexon protein comprises one or more smaller regions (e.g., hypervariable regions) of the 12 loop. In particular, preferably the smaller region of the 12 loop comprises the HVR7 region.

The "HVR7 region" preferably comprises from about amino acid 433 to about amino acid 465 of the Ad2 hexon protein [SEQ ID NO:42] (which is encoded by the sequence of SEQ ID NO:41), or the corresponding region from another adenoviral serotype, e.g., particularly the corresponding region from Ad1, Ad3, Ad5 [SEQ ID NO:44] (which is encoded by the sequence of SEQ ID NO:43), Ad6, Ad7, Ad8, Ad11, Ad12, Ad14, Ad16, Ad21, Ad34, Ad35, Ad40, Ad41, Ad48, BAV3, or MAV1, especially as reported in Crawford-Mikszsa et al., supra. In particular, preferably the deleted region comprises from about amino acid 460 to about amino acid 466 of the HVR7 region (i.e., extending one base pair outside of this region) of the Ad2 hexon protein [SEQ ID NO:46] (which is encoded by the sequence of SEQ ID NO:45), or the corresponding region from another adenoviral serotype, e.g., particularly the corresponding region from Ad1, Ad3, Ad5 [SEQ ID NO:48] (which is encoded by the sequence of SEQ ID NO:47), Ad6, Ad7, Ad8, Ad11, Ad12, Ad14, Ad16, Ad21, Ad34, Ad35, Ad40, Ad41, Ad48, BAV3, or MAV1, especially as reported in Crawford-Mikszsa et al., supra.

Along the same lines, the chimeric adenovirus hexon protein desirably comprises deletions in one or both of the aforementioned regions, i.e., the hexon protein comprises deletions in one or both of the 11 and 12 loops,

which deletions can constitute the entirety of the loop(s), or can comprise deletions of one or more smaller regions (e.g., hypervariable regions) in one or both of the hexon loops. In particular, desirably the deleted region(s) are selected from the group consisting of SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:44, SEQ ID NO:46, and SEQ ID NO:48, and equivalents and conservative variations of SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:44, SEQ ID NO:46, and SEQ ID NO:48.

An "equivalent" is a naturally occurring variation of an amino acid or nucleic acid sequence, e.g., as are observed among different strains of adenovirus. A conservative variation is a variation of an amino acid sequence that results in one or more conservative amino acid substitution(s). A "conservative amino acid substitution" is an amino acid substituted by an alternative amino acid of similar charge density, hydrophilicity/hydrophobicity, size, and/or configuration (e.g., basic, Arg and Lys; aliphatic Ala, Cys, Gly, Ile, Leu, Met and Val; aromatic, Phe, Tyr, Trp, and His; hydrophilic, Glu, Gln, Asn, and Asp; hydroxyl, Ser and Thr).

In another preferred embodiment, the nonnative amino acid sequence of the chimeric adenoviral coat protein (i.e., particularly a chimeric adenoviral fiber or hexon protein) comprises a deletion of one or more region(s) of the wild-type adenovirus coat protein (particularly the 11

and/or 12 loops, and, most particularly, the HVR1, HVR2, HVR3, HVR4, HVR5, HVR6, and/or HVR7 regions of the wild-type adenovirus hexon protein) as previously described, and further comprises a replacement of the region(s) with a spacer region preferably of from 1 to about 750 amino acids, especially of from about 1 to about 500 amino acids, and particularly of from about 1 to about 300 amino acids. It also is desirable that the region deleted and replaced comprises a smaller region less than about 200 amino acids, preferably less than about 100 amino acids, and optimally less than about 50 amino acids. The chimeric coat protein also desirably comprises a plurality of such replacements. Thus, according to the invention, the chimeric adenovirus coat protein comprises modification of one or more amino acids, and such modification is made in one or more regions which can be a smaller region. A spacer region of the aforementioned size also preferably simply can be inserted into one of the aforementioned regions (particularly into the 11 and/or 12 loop, or one or more of the aforementioned HVR1, HVR2, HVR3, HVR4, HVR5, HVR6, and HVR7 regions of the adenovirus hexon protein) in the absence of any deletion to render the resultant chimeric protein nonimmunogenic by, for instance, destroying the ability of a neutralizing antibody to interact with that particular site (e.g., by changing the spatial juxtaposition of critical amino acids with which the antibody interacts).

Optimally the spacer region comprises a nonconservative variation of the amino acid sequence of wild-type adenovirus coat protein (particularly wild-type adenovirus hexon protein) that comprises an epitope for a neutralizing antibody, and which may or may not be deleted upon the insertion of the spacer region. A "nonconservative variation" is a variation of this amino acid sequence that does not result in the creation or

recreation in the chimeric adenovirus coat protein of the epitope for a neutralizing antibody directed against the wild-type adenovirus coat protein, and, in particular, is a variation of the spacer region that results in one or more nonconservative amino acid insertion(s) or substitution(s) in this region. A "nonconservative amino acid substitution" is an amino acid substituted by an alternative amino acid of differing charge density, hydrophilicity/hydrophobicity, size, and/or configuration (e.g., a change of a basic amino acid for an acidic amino acid, a hydrophilic amino acid for a hydrophobic amino acid, and the like).

Desirably the spacer region does not interfere with the functionality of the chimeric adenovirus coat protein, particularly the chimeric adenovirus hexon or fiber protein, e.g., the ability of hexon protein to bind penton base protein or other hexon capsomeres, or the ability of penton fiber to bind penton base and/or to a cell surface receptor. Such functionality can be assessed by virus viability. Similarly, the absence of the creation or recreation of the epitope(s) for a neutralizing antibody directed against the wild-type coat (e.g., hexon and/or fiber) protein can be confirmed using techniques as described in the Examples which follow (e.g., by ensuring the antibody, which may be in a carrier fluid such as serum or other liquid, binds the wild-type adenovirus coat protein, but not the chimeric adenovirus coat protein).

Preferably the spacer region incorporated into the adenovirus coat protein (i.e., either as an insertion into the wild-type coat protein, or to replace one or more deleted region(s) of the wild-type adenovirus coat protein) comprise a series of polar and/or charged amino acids (e.g., Lys, Arg, His, Glu, Asp, and the like), or amino acids with intermediate polarity (e.g., Gln, Asn, Thr, Ser, Met, and the like). In particular, desirably

the spacer region comprises the sequence of SEQ ID NO:50 (which is encoded by the sequence of SEQ ID NO:49), and equivalents and conservative variations of SEQ ID NO:50. Alternately, the spacer region can comprise any other sequence like the FLAG octapeptide sequence of SEQ ID NO:50 that will not interfere with the functionality of the resultant chimeric protein.

In still yet another preferred embodiment, a region of a wild-type adenovirus coat protein (particularly an adenovirus hexon and/or fiber protein) is deleted and replaced with a spacer region comprising the corresponding coat protein region of another adenoviral serotype. Preferably in this embodiment the spacer region is of a different adenoviral group. For instance, preferably a region of an Ad2 coat protein can be replaced with the corresponding region of an Ad5 or Ad7 coat protein (or any other serotype of adenovirus as described above), and vice versa. It also is preferable that such a spacer region comprising the coat protein region of another adenoviral serotype is simply inserted into the corresponding coat protein region of the chimeric coat protein. In this case, the likelihood of obtaining a chimeric hexon protein that is functional can be increased by making sure that the size of the hypervariable domain resulting from such insertion approximates the size of a known hypervariable domain. For instance, the HVR1 region of Ad40 is about 30 amino acids smaller than the HVR1 region of Ad2 (as well as other adenoviruses such as Ad5, Ad8, etc.). Thus, preferably a spacer region of about 30 amino acids can be incorporated into the Ad40 HVR1 region to produce a chimeric adenovirus hexon protein. In particular, desirably the region of Ad2 (or other adenovirus) that is not present in Ad40 (i.e., approximately amino acid residues 138 to 174), or a portion thereof, is introduced

into Ad40 to produce the chimeric adenoviral hexon protein.

According to the invention, desirably the nonnative amino acid sequence of a chimeric coat protein comprises a plurality of such replacements or insertions. When the coat protein is incorporated into an adenoviral vector, preferably the entire coat protein of one adenoviral serotype can be substituted with the entire coat protein of another adenoviral serotype, as described further herein.

The region or regions of wild-type adenovirus hexon protein that are deleted and replaced by the spacer region, or into which the spacer region is inserted, can be any suitable region(s) and desirably comprise one or more of the regions described above with respect to the hexon protein deletions. For instance, preferably the one or more regions into which the spacer region is inserted or which the spacer region replaces comprises the entirety of the 11 and/or 12 loop, or a sequence selected from the group consisting of SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:44, SEQ ID NO:46, and SEQ ID NO:48, and equivalents and conservative variations of SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:44, SEQ ID NO:46, and SEQ ID NO:48.

Similarly, the spacer region itself (i.e., both for insertion as well as replacement) preferably comprises the entirety of the 11 and/or 12 loop, or a sequence selected

from the group consisting of SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:44, SEQ ID NO:46, and SEQ ID NO:48, and equivalents and conservative variations of SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:44, SEQ ID NO:46, and SEQ ID NO:48.

The fiber protein also preferably is altered in a similar fashion as described for modification of hexon protein to escape antibodies directed in particular against wild-type adenovirus fiber protein. Fiber protein sequences and methods of modifying fiber protein are known to those skilled in the art (see, e.g., Xia et al., supra; Novelli et al., Virology, 185, 365-376 (1991)). The fiber manipulations can be carried out in the absence of, or along with, modifications to the adenovirus hexon protein. In particular, preferably the fiber protein can be replaced in its entirety, or in part, with sequences of a fiber protein from a different serotype of adenovirus. Also, preferably, deletions can be made of fiber sites that constitute an epitope for a neutralizing antibody, and/or insertions can be made at the site to destroy the ability of the protein to interact with the antibody.

#### Nucleic Acid Encoding The Chimeric Adenovirus Coat Protein

Preferably the chimeric adenovirus coat protein (particularly the chimeric adenovirus hexon or fiber protein) comprises a nonnative amino acid sequence wherein

the alteration is made at the level of DNA. Thus, the invention preferably provides an isolated and purified nucleic acid encoding a chimeric adenovirus coat protein. Desirably, the invention provides an isolated and purified nucleic acid encoding a chimeric adenovirus hexon protein as defined herein, wherein the nucleic acid sequence comprises a deletion of a region (or a plurality of such deletions) that encodes from about 1 to about 750 amino acids of the wild-type adenovirus coat protein, preferably from about 1 to about 500 amino acids, and optimally from about 1 to about 300 amino acids. It also is desirable that the region deleted comprises a smaller region that encodes less than about 200 amino acids, preferably less than about 100 amino acids, and optimally less than about 50 amino acids. In particular, optimally the deletion (e.g., of an adenoviral hexon protein) comprises the entirety of the 11 and/or 12 loop, or a sequence selected from the group consisting of SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:41, SEQ ID NO:43, SEQ ID NO:45, and SEQ ID NO:47, or a sequence comprising the corresponding region from Ad1, Ad3, Ad6, Ad7, Ad8, Ad11, Ad12, Ad14, Ad16, Ad21, Ad34, Ad35, Ad40, Ad41, Ad48, BAV3, or MAV1, especially as reported in Crawford-Miksza et al., supra.

The invention also preferably provides an isolated and purified nucleic acid encoding a chimeric adenovirus hexon protein as defined herein, wherein the nucleic acid sequence comprises a deletion of one or more sequences selected from the group consisting of equivalents and conservatively modified variants of sequences that encode the entirety of the 11 and/or 12 loop, or SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID

NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:41, SEQ ID NO:43, SEQ ID NO:45, and SEQ ID NO:47, or a sequence comprising the corresponding region from Ad1, Ad3, Ad6, Ad7, Ad8, Ad11, Ad12, Ad14, Ad16, Ad21, Ad34, Ad35, Ad40, Ad41, Ad48, BAV3, or MAV1, especially as reported in Crawford-Miksza et al., supra.

With respect to the nucleic acid sequence, an "equivalent" is a variation on the nucleic acid sequence such as can occur in different strains of adenovirus, and which either does or does not result in a variation at the amino acid level. Failure to result in variation at the amino acid level can be due, for instance, to degeneracy in the triplet code. A "conservatively modified variant" is a variation on the nucleic acid sequence that results in one or more conservative amino acid substitutions. In comparison, a "nonconservatively modified variant" is a variation on the nucleic acid sequence that results in one or more nonconservative amino acid substitutions.

In another preferred embodiment, the invention provides an isolated and purified nucleic acid encoding a chimeric adenovirus coat protein wherein the nucleic acid sequence further comprises a replacement of the deleted region (or a plurality of such replacements) with a spacer nucleic acid region (i.e., the nucleic acid sequence that encodes the aforementioned "spacer region") that encodes from about 1 to about 750 amino acids of the wild-type adenovirus coat protein, preferably from about 1 to about 500 amino acids, and optimally from about 1 to about 300 amino acids. It also is desirable that the region deleted and replaced comprises a smaller region that encodes less than about 200 amino acids, preferably less than about 100 amino acids, and optimally less than about 50 amino acids.

Preferably, the spacer nucleic acid region comprises a FLAG octapeptide-encoding sequence [SEQ ID NO:49], and equivalents and conservatively modified variants of SEQ ID NO:49. Similarly, a spacer nucleic acid region can be employed that substitutes one or more coat protein encoding regions (particularly a hexon protein encoding region) of a particular adenoviral serotype with a coat protein encoding region (particularly a hexon protein encoding region) of another adenoviral serotype. Thus, preferably a spacer nucleic acid region present in a chimeric adenoviral hexon protein is selected from the group consisting of sequences that encode the entirety of the 11 and/or 12 loop, or SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:41, SEQ ID NO:43, SEQ ID NO:45, and SEQ ID NO:47, or a sequence comprising the corresponding region from Ad1, Ad3, Ad6, Ad7, Ad8, Ad11, Ad12, Ad14, Ad16, Ad21, Ad34, Ad35, Ad40, Ad41, Ad48, BAV3, or MAV1, especially as reported in Crawford-Miksza et al., supra, and equivalents and conservatively modified variants of these sequences.

As described above with respect to the chimeric adenovirus coat protein, the spacer nucleic acid region (or a plurality thereof) simply can be incorporated into the coat protein in the absence of any deletions. These manipulations can be carried out so as to produce the above-described chimeric adenovirus coat protein.

The means of making such a chimeric adenoviral coat protein (i.e., by introducing conservative or nonconservative variations at either the level of DNA or protein) are known in the art, are described in the Examples which follow, and also can be accomplished by means of various commercially available kits and vectors

(e.g., New England Biolabs, Inc., Beverly, MA; Clontech, Palo Alto, CA; Stratagene, LaJolla, CA, and the like). In particular, the ExSite™ PCR-based site-directed mutagenesis kit and the Chameleon™ double-stranded site-directed mutagenesis kit by Stratagene can be employed for introducing such mutations. Moreover, the means of assessing such mutations (e.g., in terms of effect on ability not to be neutralized by antibodies directed against wild-type hexon protein) are described in the Examples herein.

Accordingly, the present invention provides a preferred means of making a chimeric adenoviral coat protein, particularly a chimeric adenoviral hexon protein, which comprises obtaining an adenoviral genome encoding the wild-type adenovirus coat protein (e.g., the wild-type adenovirus hexon protein), and deleting one or more region(s) of the chimeric adenovirus coat protein (particularly the chimeric adenovirus hexon protein) comprising from about 1 to about 750 amino acids by modifying the corresponding nucleic acid coding sequence. Similarly, the invention provides a method of making a chimeric adenovirus coat protein (particularly a chimeric adenovirus hexon protein) which comprises obtaining an adenoviral genome encoding the wild-type adenovirus coat protein, deleting one or more region(s) of the adenovirus coat protein comprising from about 1 to about 750 amino acids by modifying the corresponding coding sequence, and replacing the deleted region(s) with a spacer region comprising from about 1 to about 300 amino acids by introducing a nucleic acid region (i.e., a "spacer nucleic acid region") that codes for same. Alternately, the spacer region preferably is simply incorporated into the coat protein (particularly the hexon protein) in the absence of any deletion. Optimally the spacer nucleic acid region encodes a nonconservative variation of the

amino acid sequence of the wild-type adenovirus coat protein. The size of the DNA used to replace the native coat protein coding sequence may be constrained, for example, by impeded folding of the coat protein or improper assembly of the coat protein into a complex (e.g., penton base/hexon complex) or virion. DNA encoding 150 amino acids or less is particularly preferred for insertion/replacement in the chimeric coat protein gene sequence, and DNA encoding 50 amino acids or less is even more preferred.

Briefly, the method of mutagenesis comprises deleting one or more regions of an adenovirus coat protein, and/or inserting into an adenovirus coat protein one or more regions with a differing amino acid sequence, particularly by manipulating the DNA sequence. Several methods are available for carrying out such manipulations of adenovirus coat protein DNA sequences; these methods further can be used in combination. The method of choice depends on factors known to those skilled in the art, e.g., the size of the DNA region to be manipulated. For instance, convenient restriction sites (which further can be introduced into a sequence) can be used to introduce or remove segments of DNA, or entire genes or coding sequences. Alternately, other methods of mutagenesis involve the hybridization of a mismatched oligonucleotide to a region of single-stranded target DNA, extending the primer, for instance, using T7 DNA polymerase or other such means to produce a double-stranded heteroduplex, and isolating the mutant strand that incorporates the mismatched oligonucleotide from the parental nonmutant strand for use as a template and in further manipulations. The mutant strand can be separated from the parental strand using various selection means known to those skilled in the art (see, e.g., Kunkel et al., Methods Enzymol., 204, 125-139 (1991), as well as the underlying

methodology employed in the Chameleon™ kit). Alternately, the parental strand can be selectively degraded, for instance, with use of enzymes that nick the nonmethylated strand of a hemi-methylated DNA molecule (e.g., *HpaII*, *MspI*, and *Sau3AI*), and by extending the mutant strand using 5-methyl-dCTP, which renders the strand resistant to cleavage by these enzymes. Along the same lines, an entirely PCR-based approach can be employed for making mutations (e.g., Kunkel, Proc. Natl. Acad. Sci., 82, 488-492 (1985); Costa et al., Nucleic Acids Res., 22, 2423 (1994)), for instance, such as the approach encompassed by the ExSite™ kit. More generally, amino acid substitutions or deletions can be introduced during PCR by incorporating appropriate mismatches in one or both primers. Once the chimeric coat protein sequence has been produced, the nucleic acid fragment encoding the sequence further can be isolated, e.g., by PCR amplification using 5' and 3' primers, or through use of convenient restriction sites.

#### Vector Comprising a Chimeric Hexon Protein

A "vector" according to the invention is a vehicle for gene transfer as that term is understood by those skilled in the art, and includes viruses, plasmids, and the like. A preferred vector is an adenovirus, particularly a virus of the family *Adenoviridae*, and desirably of the genus *Mastadenovirus* (e.g., comprised of mammalian adenoviruses) or *Aviadenovirus* (e.g., comprised of avian adenoviruses). Such an adenovirus (or other viral vector) can be transferred by its own means of effecting cell entry (e.g., by receptor-mediated endocytosis), or can be transferred to a cell like a plasmid, i.e., in the form of its nucleic acid, for instance, by using liposomes to transfer the nucleic acid, or by microinjecting or transforming the DNA into the cell. The nucleic acid vectors that can be employed for

gene transfer, particularly the adenoviral nucleic acid vectors, are referred to herein as "transfer vectors". Such nucleic acid vectors also include intermediary plasmid vectors that are employed, e.g., in the construction of adenoviral vectors.

Desirably an adenoviral vector is a serotype group C virus, preferably an Ad2 or Ad5 vector, although any other serotype adenoviral vector (e.g., group A including serotypes 12 and 31, group B including serotypes 3 and 7, group D including serotypes 8 and 30, group E including serotype 4, and group F including serotypes 40 and 41, and other Ad vectors previously described) can be employed. An adenoviral vector employed for gene transfer can be replication competent. Alternately, an adenoviral vector can comprise genetic material with at least one modification therein, which renders the virus replication deficient. The modification to the adenoviral genome can include, but is not limited to, addition of a DNA segment, rearrangement of a DNA segment, deletion of a DNA segment, replacement of a DNA segment, or introduction of a DNA lesion. A DNA segment can be as small as one nucleotide and as large as 36 kilobase pairs (i.e., the approximate size of the adenoviral genome) or, alternately, can equal the maximum amount which can be packaged into an adenoviral virion (i.e., about 38 kb). Preferred modifications to the group C adenoviral genome include modifications in the E1, E2, E3 and/or E4 regions. Similarly, an adenoviral vector can be a cointegrate, i.e., a ligation of adenoviral sequences with other sequences, such as other virus sequences, particularly baculovirus sequences, or plasmid sequences, e.g., so as to comprise a prokaryotic or eukaryotic expression vector.

In terms of an adenoviral vector (particularly a replication deficient adenoviral vector), such a vector can comprise either complete capsids (i.e., including a

viral genome such as an adenoviral genome) or empty capsids (i.e., in which a viral genome is lacking, or is degraded, e.g., by physical or chemical means). The capsid further can comprise nucleic acid linked to the surface by means known in the art (e.g., Curiel et al., Human Gene Therapy, 3, 147-154 (1992)) or can transfer non-linked nucleic acid, for instance, by adenoviral-mediated uptake of bystander nucleic acid (e.g., PCT International Application WO 95/21259).

Along the same lines, since methods are available for transferring an adenovirus in the form of its nucleic acid sequence (i.e., DNA), a vector (i.e., a transfer vector) similarly can comprise DNA, in the absence of any associated protein such as capsid protein, and in the absence of any envelope lipid. Inasmuch as techniques are available for making a RNA copy of DNA (e.g., in vitro transcription), and inasmuch as RNA viruses also can be employed as vectors or transfer vectors, a transfer vector also can comprise RNA. Thus, according to the invention whereas a vector comprises (and, further, may encode) a chimeric adenoviral coat protein, a transfer vector typically encodes a chimeric adenoviral coat protein (particularly a chimeric adenoviral hexon and/or fiber protein).

Based on this, the invention provides an adenoviral vector that comprises a chimeric coat protein (particularly a chimeric hexon and/or fiber protein) according to the invention. Preferably such a vector comprises a chimeric coat protein (particularly a chimeric adenovirus hexon protein and/or chimeric adenovirus fiber protein) as described above. Alternately, preferably the vector lacks wild-type fiber protein, e.g., the vector encodes a truncated or non-functional fiber protein, or fails to translate fiber protein. Such fiber mutations and the means of introducing fiber mutations are known to

those skilled in the art (see, e.g., Falgout et al., J. Virol., 62, 622-625 (1988)).

Of course, the chimeric adenoviral coat proteins include coat proteins in which the native (i.e., wild-type) hexon and/or fiber protein of an adenoviral vector is replaced by a hexon and or fiber amino acid sequence of a different adenoviral serotype such that the resultant adenoviral vector has a decreased ability or inability to be recognized by neutralizing antibodies directed against the corresponding wild-type coat protein. This replacement can comprise the entirety of the hexon and/or fiber amino acid sequence, or only a portion, as described above. Both proteins can be manipulated (e.g., in a single adenovirus), or only a single chimeric adenovirus coat protein can be employed, with the remaining coat proteins being wild-type.

A vector according to the invention (including a transfer vector) preferably comprises additional sequences and mutations, e.g., some that can occur within the coat protein coding sequence itself. In particular, a vector according to the invention further preferably comprises a nucleic acid encoding a passenger gene or passenger coding sequence. A "nucleic acid" is a polynucleotide (i.e., DNA or RNA). A "gene" is any nucleic acid sequence coding for a protein or an RNA molecule. Whereas a gene comprises coding sequences plus any non-coding sequences, a "coding sequence" does not include any non-coding (e.g., regulatory) DNA. A "passenger gene" or "passenger coding sequence" is any gene which is not typically present in and is subcloned into a vector (e.g., a transfer vector) according to the present invention, and which upon introduction into a host cell is accompanied by a discernible change in the intracellular environment (e.g., by an increased level of deoxyribonucleic acid (DNA), ribonucleic acid (RNA), peptide or protein, or by an

altered rate of production or degradation thereof). A "gene product" is either an as yet untranslated RNA molecule transcribed from a given gene or coding sequence (e.g., mRNA or antisense RNA) or the polypeptide chain (i.e., protein or peptide) translated from the mRNA molecule transcribed from the given gene or coding sequence. A gene or coding sequence is "recombinant" if the sequence of bases along the molecule has been altered from the sequence in which the gene or coding sequence is typically found in nature, or if the sequence of bases is not typically found in nature. According to this invention, a gene or coding sequence can be naturally occurring or wholly or partially synthetically made, can comprise genomic or complementary DNA (cDNA) sequences, and can be provided in the form of either DNA or RNA.

Non-coding sequences or regulatory sequences include promoter sequences. A "promoter" is a DNA sequence that directs the binding of RNA polymerase and thereby promotes RNA synthesis. "Enhancers" are cis-acting elements of DNA that stimulate or inhibit transcription of adjacent genes. An enhancer that inhibits transcription is also termed a "silencer". Enhancers differ from DNA-binding sites for sequence-specific DNA binding proteins found only in the promoter (which also are termed "promoter elements") in that enhancers can function in either orientation, and over distances of up to several kilobase pairs, even from a position downstream of a transcribed region. According to the invention, a coding sequence is "operably linked" to a promoter (e.g., when both the coding sequence and the promoter constitute a passenger gene) when the promoter is capable of directing transcription of that coding sequence.

Accordingly, a "passenger gene" can be any gene, and desirably either is a therapeutic gene or a reporter gene. Preferably a passenger gene is capable of being expressed

in a cell in which the vector has been internalized. For instance, the passenger gene can comprise a reporter gene, or a nucleic acid sequence which encodes a protein that can be detected in a cell in some fashion. The passenger gene also can comprise a therapeutic gene, for instance, a therapeutic gene which exerts its effect at the level of RNA or protein. Similarly, a protein encoded by a transferred therapeutic gene can be employed in the treatment of an inherited disease, such as, e.g., the cystic fibrosis transmembrane conductance regulator cDNA for the treatment of cystic fibrosis. The protein encoded by the therapeutic gene can exert its therapeutic effect by resulting in cell killing. For instance, expression of the gene in itself may lead to cell killing, as with expression of the diphtheria toxin A gene, or the expression of the gene may render cells selectively sensitive to the killing action of certain drugs, e.g., expression of the HSV thymidine kinase gene renders cells sensitive to antiviral compounds including acyclovir, gancyclovir and FIAU (1-(2-deoxy-2-fluoro-b-D-arabinofuranosil)-5-iodouracil). Moreover, the therapeutic gene can exert its effect at the level of RNA, for instance, by encoding an antisense message or ribozyme, by affecting splicing or 3' processing (e.g., polyadenylation), or by encoding a protein which acts by affecting the level of expression of another gene within the cell (i.e., where gene expression is broadly considered to include all steps from initiation of transcription through production of a processed protein), perhaps, among other things, by mediating an altered rate of mRNA accumulation, an alteration of mRNA transport, and/or a change in post-transcriptional regulation. Accordingly, the use of the term "therapeutic gene" is intended to encompass these and any other embodiments of that which is more commonly referred to as gene therapy

and is known to those of skill in the art. Similarly, the recombinant adenovirus can be used for gene therapy or to study the effects of expression of the gene (e.g., a reporter gene) in a given cell or tissue *in vitro* or *in vivo*, or for diagnostic purposes.

Also, a passenger coding sequence can be employed in the vector. Such a coding sequence can be employed for a variety of purposes even though a functional gene product may not be translated from the vector sequence. For instance, the coding sequence can be used as a substrate for a recombination reaction, e.g., to recombine the sequence with the host cell genome or a vector resident in the cell. The coding sequence also can be an "anticoding sequence," e.g., as appropriate for antisense approaches. Other means of using the coding sequence will be known to one skilled in the art.

The present invention thus provides recombinant adenoviruses comprising a chimeric hexon protein and/or a chimeric fiber protein, and which preferably additionally comprise a passenger gene or genes capable of being expressed in a particular cell. The recombinant adenoviruses can be generated by use of a vector, specifically, a transfer vector, and preferably a viral (especially an adenoviral) or plasmid transfer vector, in accordance with the present invention. Such a transfer vector preferably comprises a chimeric adenoviral hexon and/or fiber gene sequence as previously described.

Similarly, the means of constructing such a transfer vector are known to those skilled in the art. For instance, a chimeric adenovirus coat protein gene sequence can simply be ligated into the vector using convenient restriction sites. Alternately, a wild-type adenovirus gene sequence can be mutagenized to create the chimeric coat protein sequence following its subcloning into a vector. Similarly, a chimeric coat protein gene sequence

can be moved via standard molecular genetic techniques from a transfer vector into baculovirus or a suitable prokaryotic or eukaryotic expression vector (e.g., a viral or plasmid vector) for expression and evaluation of penton base binding, and other biochemical characteristics.

Accordingly, the present invention also provides recombinant baculoviral and prokaryotic and eukaryotic expression vectors comprising an aforementioned chimeric adenoviral coat protein gene sequence, which, along with the nucleic acid form of the adenoviral vector (i.e., an adenoviral transfer vector) are "transfer vectors" as defined herein. By moving the chimeric gene from an adenoviral vector to baculovirus or a prokaryotic or eukaryotic expression vector, high protein expression is achievable (approximately 5-50% of the total protein being the chimeric protein).

Similarly, adenoviral vectors (e.g., virions or virus particles) are produced using transfer vectors. For instance, an adenoviral vector comprising a chimeric coat protein according to the invention can be constructed by introducing into a cell, e.g., a 293 cell, a vector comprising sequences from the adenoviral left arm, and a vector comprising sequences from the adenoviral right arm, wherein there is a region of overlap between the sequences. As described in the Examples which follow, this methodology results in recombination between the sequences, generating a vector that comprises a portion of each of the vectors, particularly the region comprising the chimeric coat protein sequences.

The present invention thus preferably also provides a method of constructing an adenoviral vector that has a decreased ability or inability to be recognized by a neutralizing antibody directed against wild-type adenovirus hexon protein and/or fiber protein. This method comprises replacing a coat protein of the vector

(i.e., a wild-type adenovirus hexon and/or fiber protein) with the corresponding chimeric adenovirus coat protein according to the invention to produce a recombinant adenoviral vector.

The coat protein chimera-containing particles are produced in standard cell lines, e.g., those currently used for adenoviral vectors. Deletion mutants lacking the fiber gene, or possessing shortened versions of the fiber protein, similarly can be employed in vector construction, e.g., H2d1802, H2d1807, H2d11021 (Falgout et al., supra), as can other fiber mutants. The fiberless particles have been shown to be stable and capable of binding and infecting cells (Falgout et al., supra).

#### Illustrative Uses and Benefits

The present invention provides a chimeric coat protein that has a decreased ability or inability to be recognized by a neutralizing antibody directed against the corresponding wild-type coat protein, as well as vectors (including transfer vectors) comprising same. The chimeric coat protein (such as a chimeric hexon and/or fiber protein) has multiple uses, e.g., as a tool for studies in vitro of capsid structure and assembly, and capsomere binding to other proteins.

A vector (e.g., a transfer vector) comprising a chimeric coat protein can be used in strain generation, for instance, in generation of recombinant strains of adenovirus. Similarly, such a vector, particularly an adenoviral vector, can be used in gene therapy. Specifically, a vector of the present invention can be used to treat any one of a number of diseases by delivering to targeted cells corrective DNA, i.e., DNA encoding a function that is either absent or impaired, or a discrete killing agent, e.g., DNA encoding a cytotoxin that, for instance, is active only intracellularly.

Diseases that are candidates for such treatment include, but are not limited to, cancer, e.g., melanoma, glioma or lung cancers; genetic disorders, e.g., cystic fibrosis, hemophilia or muscular dystrophy; pathogenic infections, e.g., human immunodeficiency virus, tuberculosis or hepatitis; heart disease, e.g., preventing restenosis following angioplasty or promoting angiogenesis to reperfuse necrotic tissue; and autoimmune disorders, e.g., Crohn's disease, colitis or rheumatoid arthritis. In particular, gene therapy can be carried out in the treatment of diseases, disorders, or conditions that require repeat administration of the corrective DNA and/or the adenoviral vector, and thus for which current adenoviral-mediated approaches to gene therapy are less than optimal.

Moreover, such a vector, particularly an adenoviral vector, can be used to deliver material to a cell not as a method of gene therapy, but for diagnostic or research purposes. In particular, a vector comprising a chimeric adenovirus coat protein according to the invention can be employed to deliver a gene either *in vitro* or *in vivo*, for research and/or diagnostic purposes.

For instance, instead of transferring a so-called therapeutic gene, a reporter gene or some type of marker gene can be transferred instead. Marker genes and reporter genes are of use, for instance, in cell differentiation and cell fate studies, as well as potentially for diagnostic purposes. Moreover, a standard reporter gene such as a  $\beta$ -galactosidase reporter gene, a gene encoding green fluorescent protein (GFP), or a  $\beta$ -glucuronidase gene can be used *in vivo*, e.g., as a means of assay in a living host, or, for instance, as a means of targeted cell ablation (see, e.g., Minden et al., BioTechniques, 20, 122-129 (1996); Youvan, Science, 268,

264 (1995); U.S. Patent 5,432,081; Deonarain et al., Br. J. Cancer, 70, 786-794 (1994)).

Similarly, it may be desirable to transfer a gene to use a host essentially as a means of production *in vivo* of a particular protein. Along these lines, transgenic animals have been employed, for instance, for the production of recombinant polypeptides in the milk of transgenic bovine species (e.g., PCT International Application WO 93/25567). The use of an adenovirus according to the invention for gene transfer conducted for protein production *in vivo* further is advantageous in that such use should result in a reduced (if not absent) immune response as compared with the use of a wild-type adenovirus vector. Other "non-therapeutic" reasons for gene transfer include the study of human diseases using an animal model (e.g., use of transgenic mice and other transgenic animals including p53 tumor suppressor gene knockouts for tumorigenic studies, use of a transgenic model for impaired glucose tolerance and human Alzheimer's amyloid precursor protein models for the study of glucose metabolism and for the pathogenesis of Alzheimer's disease, respectively, etc.).

Furthermore, an adenoviral vector comprising a chimeric adenovirus coat protein and employed as described above is advantageous in that it can be isolated and purified by conventional means. For instance, it is likely that special cell lines will not need to be made in order to propagate adenoviruses comprising the chimeric coat proteins.

These aforementioned illustrative uses and recitation of benefits are by no means comprehensive, and it is intended that the present invention encompass such further uses which necessarily flow from, but are not explicitly recited, in the disclosure herein.

### Means of Administration

The vectors and transfer vectors of the present invention can be employed to contact cells either *in vitro* or *in vivo*. According to the invention "contacting" comprises any means by which a vector is introduced intracellularly; the method is not dependent on any particular means of introduction and is not to be so construed. Means of introduction are well known to those skilled in the art, and also are exemplified herein.

Accordingly, introduction can be effected, for instance, either *in vitro* (e.g., in an *ex vivo* type method of gene therapy or in tissue culture studies) or *in vivo* by methods that include, but are not limited to, electroporation, transformation, transduction, conjugation, triparental mating, (co-)transfection, (co-)infection, high velocity bombardment with DNA-coated microprojectiles, incubation with calcium phosphate-DNA precipitate, direct microinjection into single cells, and the like. Similarly, the vectors can be introduced by means of membrane fusion using cationic lipids, e.g., liposomes. Such liposomes are commercially available (e.g., Lipofectin®, Lipofectamine™, and the like, supplied by Life Technologies, Gibco BRL, Gaithersburg, MD). Moreover, liposomes having increased transfer capacity and/or reduced toxicity *in vivo* (see, e.g., PCT International Application WO 95/21259 and references reviewed therein) can be employed in the present invention. Other methods also are available and are known to those skilled in the art.

According to the invention, a "host" encompasses any host into which a vector of the invention can be introduced, and thus encompasses an animal, including, but not limited to, an amphibian, bird, insect, reptile, or mammal. Optimally a host is a mammal, for instance, a

rodent, primate (such as chimpanzee, monkey, ape, gorilla, orangutan, or gibbon), feline, canine, ungulate (such as ruminant or swine), as well as, in particular, a human.

Similarly, a "cell" encompasses any cell (or collection of cells) from a host into which an adenoviral vector can be introduced, e.g., preferably an epithelial cell. Any suitable organs or tissues or component cells can be targeted for vector delivery. Preferably, the organs/tissues/cells employed are of the circulatory system (e.g., heart, blood vessels or blood), respiratory system (e.g., nose, pharynx, larynx, trachea, bronchi, bronchioles, lungs), gastrointestinal system (e.g., mouth, pharynx, esophagus, stomach, intestines, salivary glands, pancreas, liver, gallbladder), urinary system (e.g., kidneys, ureters, urinary bladder, urethra), nervous system (e.g. brain and spinal cord, or special sense organs such as the eye) and integumentary system (e.g., skin). Even more preferably the cells being targeted are selected from the group consisting of heart, blood vessel, lung, liver, gallbladder, urinary bladder, and eye cells.

Thus, the present invention preferably also provides a method of genetically modifying a cell. This method preferably comprises contacting a cell with a vector comprising a chimeric adenovirus hexon protein and/or a chimeric adenovirus fiber protein, wherein desirably the vector is an adenovirus vector. The method preferably results in the production of a host cell comprising a vector according to the invention.

Moreover, the method of the invention of genetically modifying a cell can be employed in gene therapy, or for administration for diagnosis or study. The application of this method in vivo optimally comprises administering to a patient in need of gene therapy (e.g., a patient suffering from a disease, condition or disorder) a therapeutically effective amount of a recombinant adenovirus vector

according to the invention. This method preferably can be employed as part of an ongoing gene therapy regimen, e.g., wherein the vector (e.g., a recombinant adenovirus vector) comprising the chimeric adenovirus coat protein is administered following (e.g., after from about 1 week to about 2 months) administration of a therapeutically effective amount of a vector comprising either the corresponding wild-type coat protein or a coat protein of a different adenoviral serotype. Alternately, the vector comprising the chimeric adenovirus coat protein can be employed as an initial attempt at gene delivery.

One skilled in the art will appreciate that suitable methods of administering a vector (particularly an adenoviral vector) of the present invention to an animal for purposes of gene therapy (see, for example, Rosenfeld et al. (1991), supra; Jaffe et al., Clin. Res., 39(2), 302A (1991); Rosenfeld et al., Clin. Res., 39(2), 311A (1991a); Berkner, supra), chemotherapy, vaccination, diagnosis, and/or further study are available. Although more than one route can be used for administration, a particular route can provide a more immediate and more effective reaction than another route. For instance, local or systemic delivery can be accomplished by administration comprising application or instillation of the formulation into body cavities, inhalation or insufflation of an aerosol, or by parenteral introduction, comprising intramuscular, intravenous, peritoneal, subcutaneous, intradermal, as well as topical administration. Clinical trials regarding use of gene therapy vectors *in vivo* are ongoing. The methodology employed for such clinical trials as well as further technologies known to those skilled in the art can be used to administer the vector of the present invention for the purpose of research, diagnosis and/or gene therapy.

Pharmaceutically acceptable excipients also are well-known to those who are skilled in the art, and are readily available. The choice of excipient will be determined in part by the particular method used to administer the recombinant vector. Accordingly, there is a wide variety of suitable formulations for use in the context of the present invention. The following methods and excipients are merely exemplary and are in no way limiting.

Formulations suitable for oral administration can consist of (a) liquid solutions, such as an effective amount of the compound dissolved in diluents, such as water, saline, or orange juice; (b) capsules, sachets or tablets, each containing a predetermined amount of the active ingredient, as solids or granules; (c) suspensions in an appropriate liquid; and (d) suitable emulsions. Tablet forms can include one or more of lactose, mannitol, corn starch, potato starch, microcrystalline cellulose, acacia, gelatin, colloidal silicon dioxide, croscarmellose sodium, talc, magnesium stearate, stearic acid, and other excipients, colorants, diluents, buffering agents, moistening agents, preservatives, flavoring agents, and pharmacologically compatible excipients. Lozenge forms can comprise the active ingredient in a flavor, usually sucrose and acacia or tragacanth, as well as pastilles comprising the active ingredient in an inert base, such as gelatin and glycerin, or sucrose and acacia, emulsions, gels, and the like containing, in addition to the active ingredient, such excipients as are known in the art.

A vector of the present invention (including an adenoviral vector and a transfer vector), alone or in combination with other suitable components, can be made into aerosol formulations to be administered via inhalation. These aerosol formulations can be placed into pressurized acceptable propellants, such as dichlorodifluoromethane, propane, nitrogen, and the like.

They may also be formulated as pharmaceuticals for non-pressured preparations such as in a nebulizer or an atomizer.

Formulations suitable for parenteral administration include aqueous and non-aqueous, isotonic sterile injection solutions, which can contain anti-oxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. The formulations can be presented in unit-dose or multi-dose sealed containers, such as ampules and vials, and can be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid excipient, for example, water, for injections, immediately prior to use. Extemporaneous injection solutions and suspensions can be prepared from sterile powders, granules, and tablets of the kind previously described.

Additionally, a vector of the present invention can be made into suppositories by mixing with a variety of bases such as emulsifying bases or water-soluble bases.

Formulations suitable for vaginal administration can be presented as pessaries, tampons, creams, gels, pastes, foams, or spray formulas containing, in addition to the active ingredient, such carriers as are known in the art to be appropriate.

The dose administered to an animal, particularly a human, in the context of the present invention will vary with the gene of interest, the composition employed, the method of administration, the particular site and organism undergoing administration, and the reason for the administration (e.g., gene therapy, diagnosis, means of producing a protein, further study, etc). Generally, the "effective amount" of the composition is such as to

produce the desired effect in a host which can be monitored using several end-points known to those skilled in the art. For example, one desired effect might comprise effective nucleic acid transfer to a host cell. Such transfer can be monitored in terms of a therapeutic effect (e.g., alleviation of some symptom associated with the disease or syndrome being treated), or by further evidence of the transferred gene or coding sequence or its expression within the host (e.g., using the polymerase chain reaction, Northern or Southern hybridizations, or transcription assays to detect the nucleic acid in host cells, or using immunoblot analysis, antibody-mediated detection, or particularized assays to detect protein or polypeptide encoded by the transferred nucleic acid, or impacted in level or function due to such transfer). One such particularized assay described in the Examples which follow includes an assay for expression of a chloramphenicol acetyl transferase reporter gene.

Generally, to ensure effective transfer of the vectors of the present invention, it is preferable that from about 1 to about 5,000 copies of the vector be employed per cell to be contacted, based on an approximate number of cells to be contacted in view of the given route of administration. It is even more preferable that from about 1 to about 300 plaque forming units (pfu) enter each cell. However, this is just a general guideline which by no means precludes use of a higher or lower amount of a component, as might be warranted in a particular application, either *in vitro* or *in vivo*. For example, the actual dose and schedule can vary depending on whether the composition is administered in combination with other pharmaceutical compositions, or depending on interindividual differences in pharmacokinetics, drug disposition, and metabolism. Similarly, amounts can vary in *in vitro* applications depending on the particular cell

type utilized or the means by which the vector is transferred. One skilled in the art easily can make any necessary adjustments in accordance with the necessities of the particular situation.

The following examples further illustrate the present invention and, of course, should not be construed as in any way limiting its scope.

#### Example 1

This example describes experiments investigating adenoviral anti-vector neutralizing immunity.

To clarify the phenomenon of neutralizing immunity, an animal having circulating antibodies to one adenoviral vector type received intratracheal administration of another serotype adenoviral vector, and gene expression commanded by the second vector was monitored. Specifically, either an Ad4 or Ad5 wild-type vector was administered to the lungs of Sprague-Dawley rats. Ten days later, an Ad5 reporter vector was administered to the lungs of the same animals. This reporter vector, which is referred to herein as the "pure 5" vector, comprises an E1<sup>-</sup>E3<sup>-</sup> type 5 adenoviral vector which expresses the chloramphenicol acetyl transferase (CAT) gene driven by the cytomegalovirus early/intermediate promoter/enhancer (CMV) (i.e., AdCMVCATgD described in Kass-Eisler et al., Proc. Natl. Acad. Sci., 15, 11498-11502 (1993)).

About twenty-four hours following administration of the "pure 5" vector, CAT activity was measured in homogenized lung tissue using a CAT assay as previously described (Kass Eisler et al. (1993), supra). CAT activity was monitored at various times thereafter up to 10 days following introduction of the "pure 5" vector. CAT activity was determined relative to the "pure 5" vector administered to naive animals (i.e., expression measured under this condition was considered 100%). The

results of these studies are set out in **Table 1**, and are further reported in Mastrangeli et al., Human Gene Therapy, 1, 79-87 (1996).

<b>Table 1.</b> Effect of anti-serotype 4 (group E) neutralizing antibodies on the ability of a "pure 5" adenoviral vector to transfer a CAT reporter gene to the lung		
<b>Time (0 hours)</b>	<b>Time (10 days)</b>	<b>CAT Activity</b>
--	--	0%
--	pure 5	100%
Ad5	pure 5	0%
Ad4	pure 5	105±10%

These results confirm that in the presence of neutralizing antibodies elicited against one adenoviral group (e.g., against group E, serotype 4), it is possible to efficiently transfer and express a gene *in vivo* using an adenoviral vector derived from another group (e.g., derived from group C, serotype 5). Neutralizing immunity evoked against one serotype group does not protect against infection by another group of adenovirus. These data support the paradigm of alternating adenoviral vectors derived from different subgroups as a strategy to circumvent anti-adenoviral humoral immunity.

#### Example 2

The predominant epitopes that evoke neutralizing immunity are located on the fiber and hexon, but mainly on hexon. Based on this, the effect of switching the fiber protein was investigated. A vector was constructed that was identical to the "pure 5" vector except that the fiber gene was switched from a serotype 5, group C fiber to a

serotype 7, group B fiber. The resultant vector is referred to herein as the "5 base/7 fiber" vector.

The Ad5/Ad7 fiber construct was generated as shown in **Figure 1**. An approximately 2.7 kb (Ad5 28689-31317 bp) fragment in pAd70-100 was replaced with a PacI linker (pAd70-100dlE3.Pac). A BamHI linker was inserted at a MunI site as indicated in **Figure 2** to produce pAd70-100dlE3.Pac.Bam. A PCR-amplified PacI-BamHI fragment of approximately 1.1 kb containing the Ad7 fiber gene was inserted into pAd70-100dlE3.Pac.Bam to produce pAd70-100dlE3.fiber7.

In order to assess the ability of the Ad5 virus with Ad7 fiber to infect cells *in vitro* and *in vivo*, reporter gene assays were performed. A replication-defective recombinant adenoviral reporter vector designated AdCMV-CATNeo was used in the reporter gene assay. The reporter vector consists of the adenoviral origin of replication and viral packaging sequences, a combination of strong eukaryotic promoter (cytomegalovirus or CMV-1) and splicing elements, the bacterial chloramphenicol acetyl transferase (CAT) gene sequence, the mouse  $\beta^{\text{maj}}$ -globin poly(A) site, the neomycin gene sequence (Neo), and sufficient adenoviral DNA to allow for overlap recombination.

The reporter vector was used to generate AdCMV-CATNeo, AdCMV-CATNeo-dlE3 (AdCMV-CATNeo + pAd70-100dlE3) and AdCMV-CATNeo-dlE3-Fiber7 (AdCMV-CATNeo + pAd70-100dlE3.Fiber7) viruses. Each virus was grown in large scale, i.e., a one liter suspension of human embryonic kidney 293 cells, to yield virus at a concentration of  $10^{12}$  particles/ml. A549 cells were infected with an estimated 100, 300 or 1,000 particles/cell of one of the three viruses. After 48 hours, the cells were harvested and lysates were prepared as described in Kass-Eisler et al.

(1993), supra. Using 50  $\mu$ l of each lysate, CAT assays were performed and acetylated chloramphenicol products were separated by thin layer chromatography using chloroform:methanol (95:5). The results of the assays confirm that each virus was able to infect cells and express gene products at appropriate levels. Accordingly, the virus in which the native fiber was replaced with a nonnative fiber could infect cells and express genes like the parental virus.

Following this study, adult Sprague-Dawley rats were infected with  $10^8$  viral particles by direct cardiac injection as described in Kass-Eisler et al. (1993), supra. Five days later, the rats were sacrificed, cardiac lysates were prepared, and CAT assays were performed. The amount of the CAT gene product produced was compared between the dlE3 and dlE3-Fiber7 viruses. Results indicated that both viruses were able to infect cells *in vivo*. The replacement of the wild-type Ad5 fiber gene with that of Ad7 did not impair the ability of the virus to infect cells. Accordingly, the virus in which the native fiber was replaced with a nonnative fiber could also infect cells and express genes like the parental virus *in vivo*. These results support the utility of adenovirus with chimeric fiber in the context of gene therapy.

### Example 3

This example describes the effect on neutralizing immunity of switching the fiber protein of an adenovirus from one serotype to another.

The "pure 5" and "5 base/7 fiber" vectors described in the preceding Example were administered to Sprague-Dawley rats which either were naive or pre-immunized against wild-type Ad5. For these experiments, wild-type Ad5 or wild-type Ad7 ( $6 \times 10^9$  particles in phosphate

buffered saline (PBS)) was administered intraperitoneally as a primary inoculation. Seventeen days later, serum samples were taken, and about  $6 \times 10^9$  particles in about 50  $\mu$ l of PBS was injected. At about 120 hours following injection the animals were sacrificed, serum and heart tissue were harvested, and heart tissue was processed for CAT assays as previously described (Kass-Eisler et al. (1993), supra). CAT assays also were performed on heart lysates of rat hearts infected with the "pure 5" vector or "5 base/7 fiber" vector alone.

Administration of either vector to naive animals resulted in comparable levels of CAT in heart tissue. In comparison, administration of either the "pure 5" vector or the "5 base/7 fiber" vector to the animals that were pre-immunized against the "pure 5" vector resulted in a reduction of CAT levels by more than two orders of magnitude as compared with mock-infected controls. These and further results are reported in Gall et al., J. Virol., 70, 2116-2163 (1996).

These results confirm that switching the fiber from that of adenoviral serotype 5 group C vector to that of an adenoviral serotype 7 group B vector by itself is insufficient to allow the vector to escape neutralizing antibodies generated against an adenoviral vector comprising Ad5 fiber. These results imply that antibodies against adenoviral structures other than fiber also are important in the process of neutralizing immunity. Furthermore, whereas switching the fiber serotype to another serotype may be insufficient in and of itself to allow an adenovirus to escape immune detection, such switching when done in combination with removal of other epitopes may be desirable, for instance, to reduce an immune response.

Example 4

This example describes the construction of adenovirus vectors wherein the neutralizing immunity-evoking epitopes have been modified. In particular, this example describes vectors comprising chimeric adenoviral hexon protein, wherein the hexon neutralizing immunity-evoking epitopes are modified.

The results of the prior example indicate that it is possible to develop vectors for repeat administration in gene therapy from non-group C adenovirus, thus circumventing pre-existing neutralizing immunity. As another strategy, the dominant neutralizing immunity-evoking epitopes on existing group C vectors can be modified to render the vectors less susceptible (or "stealth") to the existing neutralizing immunity. For instance, adenoviral type 5-based E1<sup>-</sup> E3<sup>-</sup> CAT-expressing vectors can be constructed that have the same genetic composition as the "pure 5" and "5 base/7 fiber" vectors described above, except for possessing a gene encoding a chimeric hexon that is not recognized by pre-existing anti-type 5 neutralizing immunity.

To derive the vectors, the chimeric hexon gene present in the "pure 5" parental vector can be modified, in particular, 11 and/or 12 can be altered. The hexon modifications that can be made on the "pure 5" CAT vector, or other adenoviral vector (such as any other adenoviral serotype vector), include, but are not limited to: (1) hexon with 11 deleted in its entirety; (2) hexon with 12 deleted in its entirety; (3) hexon with both 11 and 12 deleted; (4) hexon with any one or more of HVR1, HVR2, HVR3, HVR4, HVR5, HVR6, or HVR7, deleted; (5)-(8) hexon with a FLAG octamer epitope (i.e., Asp Tyr Lys Asp Asp Asp Asp Lys [SEQ ID NO:50]; Hopp et al., Biotechnology, 6, 1205-1210 (1988)) substituted for 11, 12, or both 11 and 12, or any one or more of HVR1, HVR2, HVR3, HVR4, HVR5,

HVR6 or HVR7; (9)-(12) hexon with a FLAG octamer epitope [SEQ ID NO:50] inserted into 11, 12, or both 11 and 12; (13)-(16) hexon with comparable epitopes from Ad7 (group B) (GenBank® Data Bank Accession Number x76551 for Ad7 hexon, and Number M73260 for Ad5 hexon) or Ad2, or any other adenoviral serotype, substituted for 11, 12, both 11 and 12, respectively, or for any one or more of HVR1, HVR2, HVR3, HVR4, HVR5, HVR6, or HVR7; (17)-(20) hexon with comparable epitopes from Ad7 (group B) (GenBank® Data Bank Accession Number x76551 for Ad7 hexon, and Number M73260 for Ad5 hexon) or Ad2, or any other adenoviral serotype, inserted into 11, 12, both 11 and 12, respectively, or any one or more of HVR1, HVR2, HVR3, HVR4, HVR5, HVR6, or HVR7; and (21) complete substitution of the hexon from Ad2 or another adenoviral serotype, for the Ad5 hexon. The use of the FLAG octamer epitope provides a sequence for incorporation in the chimeric hexon protein that is different from the Ad5 hexon loop sequences, and also provides a positive control using available specific anti-FLAG antibodies (Hopp et al., supra).

These chimeric hexon proteins (and vectors containing them) can be made in several steps. To modify the hexon in the "pure 5" vector, a viral or plasmid vector can be constructed to contain the hexon type 5 coding sequence in a cassette that can be easily modified. The hexon is read off the 1 strand of the L3 transcription unit, i.e., map units 51.6 to 59.7, comprising a region of about 2.9 kb. The two other transcripts that also are encoded by L3 -- i.e., polypeptide VI and a 23 kDa protein -- do not overlap the hexon coding sequence. Moreover, there are no other coding sequences on the r strand that would be altered by the modification of the hexon coding sequence.

Thus, all the modifications of the type 5 hexon can be made using a "hexon 5 cassette" comprised of an

approximate 6.7 kb SfiI-SfiI fragment of the "pure 5" CAT vector. SfiI cuts Ad5 into 3 fragments, the center 6.7 kb fragment (i.e., comprising about 16,282 to 22,992 base pairs, as identified by agarose gel electrophoresis) of which contains all of the L3 region plus some overlap. The "hexon 5 cassette" can be subcloned into a commercially available vector having restriction sites and the like making the vector easily manipulable in terms of modification and recovery of subcloned sequences. One such vector appropriate for subcloning is either the SK or KS version of the pBlueScript® phagemid (Stratagene, LaJolla, CA).

The "hexon 5 cassette" can be mutagenized to generate site-specific mutations in the cloned DNA segment. Several methods are available for carrying out site-specific mutagenesis. The 11 and 12 deletions, insertions, or replacements (or deletions, insertions, or replacements in HVR1, HVR2, HVR3, HVR4, HVR5, HVR6, or HVR7 regions contained therein) can be made by deleting the relevant sequences using restriction enzymes that cut uniquely within the vector inserts, or other similar means, e.g., by ligating in an end-polished, or otherwise modified, PCR product. Alternately, the hexon sequence contained in the hexon 5 cassette can be modified, e.g., using single-stranded mutagenesis in M13mp8 or some other convenient vector, and using appropriate oligonucleotides encompassing the flanking sequences for identification of plaques as described by Crompton et al., supra. Alternately, a commercially available kit such as the ExSite™ PCR-based site-directed mutagenesis kit and the Chameleon™ double-stranded site-directed mutagenesis kit by Stratagene can be used to introduce insertions, point mutations, or deletions into the chimeric hexon sequence without any need for subcloning into an M13, or other special vector.

Similarly, the FLAG octapeptide sequence (Hopp et al., supra) can be introduced into the vectors (i.e., in the presence or absence of any deletion) by inserting the relevant 24 base pair sequence (GAY TAY AAR GAY GAY GAY GAY AAR [SEQ ID NO:50], wherein Y is C or T/U, and R is A or G)). The replacement of Ad5 hexon loop epitopes with comparable sequences of Ad7, Ad2, or any other adenoviral serotype, or an incorporation of these sequences in the absence of any deletion, can be accomplished by using unique restriction sites, or using one of the aforementioned means of mutagenesis. This usefully creates new serotypes of adenoviral vectors. For example, The replacement of the wildtype hexon protein of Ad5 with the chimeric Ad5 hexon comprising Ad7 hexon loops 1 and 2 gives rise to an adenoviral vector that is effectively neutralized by Ad7 neutralizing antibodies (i.e., neutralizing antibodies raised in response to Ad7 inoculation of a naïve animal), but not by Ad5 neutralizing antibodies.

Moreover, both hypervariable loops 1 and 2 can be deleted from a serotype 5 or another serotype adenoviral vector. Adenoviral vectors and there genomes comprising these deletions are useful as a starting point to create other adenoviral vectors having loop replacements, as a tool for studying hexon structure-function relationships, and under some circumstances as a gene transfer vector with limited vulnerability to the adaptive immune system.

#### Example 5

This example describes the method of replacing the hexon protein of one serotype adenoviral vector with the hexon protein of another serotype adenoviral vector to generate a recombinant adenovirus. As representative of this method, the hexon protein of an Ad5 vector was replaced with the hexon protein of an Ad2 vector. This

example also describes the method of incorporating the chimeric hexon proteins of the preceding Example into a vector to make a recombinant adenovirus.

Using standard molecular biology techniques, the Ad5 hexon gene open reading frame (ORF) was replaced with the Ad2 hexon gene ORF in such a fashion so as to maintain the proper Ad5 sequences upstream and downstream of the hexon gene. Adenoviral vectors comprising modified or chimeric hexon proteins can be constructed by homologous recombination using standard techniques and human embryonic kidney 293 cells (see, e.g., Rosenfeld et al. (1991), supra; Rosenfeld et al. (1992), supra). For instance, map units 0 to 57.3 of dlAd5NCAT (Gall et al., supra) can be isolated by Bsu36I digestion, and map units 58.4 to 100 of dlAd5NCAT can be isolated by DrdI digestion. These DNA fragments can be transfected into 293 cells along with pH5-2.

A neutralizing antibody directed against the parental vector can be employed to facilitate the generation of hexon replacement constructs. For example, when replacing the loop 1 and loop 2 regions of an Ad5 vector with Ad7 loop sequences, anti-Ad5 neutralizing polyclonal or monoclonal antibodies (directed against the loops 1 and 2 of Ad5 hexon) can be added to the medium of cells in which the chimeric vector is being propagated. The presence of the Ad5 neutralizing antibodies substantially blocks the propagation of the undesired wildtype Ad5 vector(s), while the chimeric vector is unaffected. Furthermore, the recombinant vectors comprising a chimeric hexon ORF can be generated by homologous recombination using a plasmid that carries a marker gene, such as Green Fluorescent Protein (GFP), adjacent to the chimeric or novel hexon ORF (e.g., between the fiber and hexon genes). In this way, genomes that could harbor the chimeric hexon gene should also harbor the marker gene. The marker gene

would then be expressed as a late protein, so that cells that potentially comprise the desired adenoviral genome can be easily identified.

Similarly, vectors (particularly adenoviral vectors) can be constructed that have the aforementioned hexon modifications, and which have further modifications, for instance, in the adenoviral fiber coding sequences. This can be accomplished by making the hexon modifications described above, and using different parental plasmids for homologous recombination, such as parental plasmids comprising mutations in fiber coding sequences. In particular, the "5 base/7 fiber" vector can be employed as a starting vector for vector construction.

All of the viral vectors prepared according to this example can be plaque-purified, amplified, and further purified using standard methods (Rosenfeld et al. (1991), supra; Rosenfeld et al. (1992), supra).

#### Example 6

This example describes a characterization of the activity *in vitro* and *in vivo* of the vectors described in the preceding Examples.

Each of the viruses prepared as described in the preceding Examples can be evaluated *in vitro* and *in vivo* using standard methods as previously described (e.g., Kass-Eisler et al., supra), and as set forth herein. In particular, for the *in vitro* studies, the various vectors along with control vectors (e.g., the "pure 5" and "5 base/7 fiber" vectors, and the Ad5 wild-type vector) can be added to human lung carcinoma A549 cells alone, or in the presence of dilutions of serum from hosts infected with Ad5, Ad7, "pure 5" CAT vector, or "5 base/7 fiber" CAT vector, or anti-FLAG epitope serum. The cells are then evaluated for CAT activity to determine the ability

of antibodies present in the serum to block gene expression.

The *in vivo* studies can be carried out in Sprague-Dawley rats. The Sprague-Dawley rat as opposed to the mouse or cotton rat is preferred for these experiments since the rat is non-permissive, and the wild-type adenovirus cannot replicate in this host. Accordingly, immunizations can be carried out using wild-type viruses (e.g., wild-type Ad5 or Ad7), the "pure 5" CAT vector, and the "5 base/7 fiber" CAT vector by intravenous administration (e.g., Kass-Eisler et al., supra). At various times ranging from about one to about four weeks later, the vector of interest can be administered intravenously or directly into the airways of the host. Whereas intravenous administration allows an assessment of the "worst case scenario" (i.e., wherein the vector is in immediate contact with the circulating humoral immune system, and thus the strongest immune response is to be expected), introduction in the airways of the host allows an evaluation of a compartmentalized and mucosal humoral immune response.

CAT activity can be quantified as previously described in all the relevant organs, e.g., liver, heart, and lung for intravenous administration, and lung only for respiratory administration. Appropriate standards can be used to compensate for variations in organ expression of CAT activity (see e.g., Kass-Eisler et al., Gene Therapy, 2 395-402 (1994)). The *in vitro* and *in vivo* results can be compared and assessed using standard statistical methods.

All of the references cited herein, including the GenBank® Data Bank sequence information, are hereby incorporated in their entireties by reference.

While this invention has been described with emphasis upon preferred embodiments, it will be obvious to those of ordinary skill in the art that the preferred embodiments can be varied. It is intended that the invention can be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications encompassed within the spirit and scope of the appended claims.

## SEQUENCE LISTING

## (1) GENERAL INFORMATION:

## (i) APPLICANT:

(A) NAME: CORNELL RESEARCH FOUNDATION, INC.  
(B) STREET: 20 Thornwood Drive, Suite 105  
(C) CITY: Ithaca  
(D) STATE: New York  
(E) COUNTRY: US  
(F) POSTAL CODE (ZIP): 14850  
(G) TELEPHONE: 607-257-1081  
(H) TELEFAX: 607-257-1015

(A) NAME: GENVEC, INC.  
(B) STREET: 12111 Parklawn Drive  
(C) CITY: Rockville  
(D) STATE: Maryland  
(E) COUNTRY: US  
(F) POSTAL CODE (ZIP): 20852  
(G) TELEPHONE: 301-816-0396  
(H) TELEFAX: 301-816-0085

(A) NAME: CRYSTAL, RONALD G.  
(B) STREET: 13712 Canal Vista Court  
(C) CITY: Potomac  
(D) STATE: Maryland  
(E) COUNTRY: US  
(F) POSTAL CODE (ZIP): 20854

(A) NAME: FALCK-PEDERSEN, ERIK  
(B) STREET: 8714 Buena Vista Drive  
(C) CITY: Dobbs Ferry  
(D) STATE: New York  
(E) COUNTRY: US  
(F) POSTAL CODE (ZIP): 10522

(A) NAME: GALL, JASON  
(B) STREET: 420 E. 70th Street, #10F  
(C) CITY: New York  
(D) STATE: New York  
(E) COUNTRY: US  
(F) POSTAL CODE (ZIP): 10021

(A) NAME: KOVESDI, IMRE  
(B) STREET: 7713 Warbler Lane  
(C) CITY: Rockville  
(D) STATE: Maryland  
(E) COUNTRY: US  
(F) POSTAL CODE (ZIP): 20855

(A) NAME: WICKHAM, THOMAS J.  
(B) STREET: 2106 Hutchinson Grove Court  
(C) CITY: Falls Church  
(D) STATE: Virginia  
(E) COUNTRY: US  
(F) POSTAL CODE (ZIP): 22043

(ii) TITLE OF INVENTION: CHIMERIC ADENOVIRAL COAT PROTEIN AND METHODS  
OF USING SAME

(iii) NUMBER OF SEQUENCES: 56

(iv) COMPUTER READABLE FORM:

59

- (A) MEDIUM TYPE: Floppy disk  
 (B) COMPUTER: IBM PC compatible  
 (C) OPERATING SYSTEM: PC-DOS/MS-DOS  
 (D) SOFTWARE: PatentIn Release #1.0, Version #1.30 (EPO)

## (vi) PRIOR APPLICATION DATA:

- (A) APPLICATION NUMBER: US 8-816346  
 (B) FILING DATE: 13-MAR-1997

## (2) INFORMATION FOR SEQ ID NO:1:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2907 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: double  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: DNA (genomic)

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

ATG GCT ACC CCT TCG ATG ATG CCG CAG TGG TCT TAC ATG CAC ATC TCG	48
Met Ala Thr Pro Ser Met Met Pro Gln Trp Ser Tyr Met His Ile Ser	
1 5 10 15	
GGC CAG GAC GCC TCG GAG TAC CTG AGC CCC GGG CTG GTG CAG TTT GCC	96
Gly Gln Asp Ala Ser Glu Tyr Leu Ser Pro Gly Leu Val Gln Phe Ala	
20 25 30	
CGC GCC ACC GAG ACG TAC TTC AGC CTG AAT AAC AAG TTT AGA AAC CCC	144
Arg Ala Thr Glu Thr Tyr Phe Ser Leu Asn Asn Lys Phe Arg Asn Pro	
35 40 45	
ACG GTG GCA CCT ACG CAC GAC GTA ACC ACA GAC CGG TCC CAG CGT TTG	192
Thr Val Ala Pro Thr His Asp Val Thr Thr Asp Arg Ser Gln Arg Leu	
50 55 60	
ACG CTG CGG TTC ATC CCT GTG GAC CGC GAG GAT ACC GCG TAC TCG TAC	240
Thr Leu Arg Phe Ile Pro Val Asp Arg Glu Asp Thr Ala Tyr Ser Tyr	
65 70 75 80	
AAA GCG CGG TTC ACC CTG GCT GTG GGT GAC AAC CGT GTG CTT GAT ATG	288
Lys Ala Arg Phe Thr Leu Ala Val Gly Asp Asn Arg Val Leu Asp Met	
85 90 95	
GCT TCC ACG TAC TTT GAC ATC CGC GGC GTG CTG GAC AGG GGG CCT ACT	336
Ala Ser Thr Tyr Phe Asp Ile Arg Gly Val Leu Asp Arg Gly Pro Thr	
100 105 110	
TTT AAG CCC TAC TCC GGC ACT GCC TAC AAC GCT CTA GCT CCC AAG GGC	384
Phe Lys Pro Tyr Ser Gly Thr Ala Tyr Asn Ala Leu Ala Pro Lys Gly	
115 120 125	
GCT CCT AAC TCC TGT GAG TGG GAA CAA ACC GAA GAT AGC GGC CGG GCA	432
Ala Pro Asn Ser Cys Glu Trp Glu Gln Thr Glu Asp Ser Gly Arg Ala	
130 135 140	
GTT GCC GAG GAT GAA GAA GAG GAA GAT GAA GAT GAA GAA GAG GAA GAA	480
Val Ala Glu Asp Glu Glu Glu Glu Asp Glu Asp Glu Glu Glu Glu Glu	
145 150 155 160	
GAA GAG CAA AAC GCT CGA GAT CAG GCT ACT AAG AAA ACA CAT GTC TAT	528
Glu Glu Gln Asn Ala Arg Asp Gln Ala Thr Lys Lys Thr His Val Tyr	
165 170 175	

GCC CAG GCT CCT TTG TCT GGA GAA ACA ATT ACA AAA AGC GGG CTA CAA Ala Gln Ala Pro Leu Ser Gly Glu Thr Ile Thr Lys Ser Gly Leu Gln 180 185 190	576
ATA GGA TCA GAC AAT GCA GAA ACA CAA GCT AAA CCT GTA TAC GCA GAT Ile Gly Ser Asp Asn Ala Glu Thr Gln Ala Lys Pro Val Tyr Ala Asp 195 200 205	624
CCT TCC TAT CAA CCA GAA CCT CAA ATT GGC GAA TCT CAG TGG AAC GAA Pro Ser Tyr Gln Pro Glu Pro Gln Ile Gly Glu Ser Gln Trp Asn Glu 210 215 220	672
GCT GAT GCT AAT GCG GCA GGA GGG AGA GTG CTT AAA AAA ACA ACT CCC Ala Asp Ala Asn Ala Ala Gly Gly Arg Val Leu Lys Lys Thr Thr Pro 225 230 235 240	720
ATG AAA CCA TGC TAT GGA TCT TAT GCC AGG CCT ACA AAT CCT TTT GGT Met Lys Pro Cys Tyr Gly Ser Tyr Ala Arg Pro Thr Asn Pro Phe Gly 245 250 255	768
GGT CAA TCC GTT CTG GTT CCG GAT GAA AAA GGG GTG CCT CTT CCA AAG Gly Gln Ser Val Leu Val Pro Asp Glu Lys Gly Val Pro Leu Pro Lys 260 265 270	816
GTT GAC TTG CAA TTC TTC TCA AAT ACT ACC TCT TTG AAC GAC CGG CAA Val Asp Leu Gln Phe Phe Ser Asn Thr Thr Ser Leu Asn Asp Arg Gln 275 280 285	864
GGC AAT GCT ACT AAA CCA AAA GTG GTT TTG TAC AGT GAA GAT GTA AAT Gly Asn Ala Thr Lys Pro Lys Val Val Leu Tyr Ser Glu Asp Val Asn 290 295 300	912
ATG GAA ACC CCA GAC ACA CAT CTG TCT TAC AAA CCT GGA AAA GGT GAT Met Glu Thr Pro Asp Thr His Leu Ser Tyr Lys Pro Gly Lys Gly Asp 305 310 315 320	960
GAA AAT TCT AAA GCT ATG TTG GGT CAA CAA TCT ATG CCA AAC AGA CCC Glu Asn Ser Lys Ala Met Leu Gly Gln Gln Ser Met Pro Asn Arg Pro 325 330 335	1008
AAT TAC ATT GCT TTC AGG GAC AAT TTT ATT GGC CTA ATG TAT TAT AAC Asn Tyr Ile Ala Phe Arg Asp Asn Phe Ile Gly Leu Met Tyr Tyr Asn 340 345 350	1056
AGC ACT GGC AAC ATG GGT GTT CTT GCT GGT CAG GCA TCG CAG CTA AAT Ser Thr Gly Asn Met Gly Val Leu Ala Gly Gln Ala Ser Gln Leu Asn 355 360 365	1104
GCC GTG GTA GAT TTG CAA GAC AGA AAC ACA GAG CTG TCC TAT CAA CTC Ala Val Val Asp Leu Gln Asp Arg Asn Thr Glu Leu Ser Tyr Gln Leu 370 375 380	1152
TTG CTT GAT TCC ATA GGT GAT AGA ACC AGA TAT TTT TCT ATG TGG AAT Leu Leu Asp Ser Ile Gly Asp Arg Thr Arg Tyr Phe Ser Met Trp Asn 385 390 395 400	1200
CAG GCT GTA GAC AGC TAT GAT CCA GAT GTT AGA ATC ATT GAA AAC CAT Gln Ala Val Asp Ser Tyr Asp Pro Asp Val Arg Ile Ile Glu Asn His 405 410 415	1248
GGA ACT GAG GAT GAA TTG CCA AAT TAT TGT TTT CCT CTT GGG GGT ATT Gly Thr Glu Asp Glu Leu Pro Asn Tyr Cys Phe Pro Leu Gly Gly Ile 420 425 430	1296

GGG	GTA	ACT	GAC	ACC	TAT	CAA	GCT	ATT	AAG	GCT	AAT	GGC	AAT	GGC	TCA	1344
Gly	Val	Thr	Asp	Thr	Tyr	Gln	Ala	Ile	Lys	Ala	Asn	Gly	Asn	Gly	Ser	
		435					440					445				
GGC	GAT	AAT	GGA	GAT	ACT	ACA	TGG	ACA	AAA	GAT	GAA	ACT	TTT	GCA	ACA	1392
Gly	Asp	Asn	Gly	Asp	Thr	Thr	Trp	Thr	Lys	Asp	Glu	Thr	Phe	Ala	Thr	
		450				455					460					
CGT	AAT	GAA	ATA	GGA	GTG	GGT	AAC	AAC	TTT	GCC	ATG	GAA	ATT	AAC	CTA	1440
Arg	Asn	Glu	Ile	Gly	Val	Gly	Asn	Asn	Phe	Ala	Met	Glu	Ile	Asn	Leu	
465					470					475					480	
AAT	GCC	AAC	CTA	TGG	AGA	AAT	TTC	CTT	TAC	TCC	AAT	ATT	GCG	CTG	TAC	1488
Asn	Ala	Asn	Leu	Trp	Arg	Asn	Phe	Leu	Tyr	Ser	Asn	Ile	Ala	Leu	Tyr	
				485					490					495		
CTG	CCA	GAC	AAG	CTA	AAA	TAC	AAC	CCC	ACC	AAT	GTG	GAA	ATA	TCT	GAC	1536
Leu	Pro	Asp	Lys	Leu	Lys	Tyr	Asn	Pro	Thr	Asn	Val	Glu	Ile	Ser	Asp	
			500					505					510			
AAC	CCC	AAC	ACC	TAC	GAC	TAC	ATG	AAC	AAG	CGA	GTG	GTG	GCT	CCC	GGG	1584
Asn	Pro	Asn	Thr	Tyr	Asp	Tyr	Met	Asn	Lys	Arg	Val	Val	Ala	Pro	Gly	
		515					520					525				
CTT	GTA	GAC	TGC	TAC	ATT	AAC	CTT	GGG	GCG	CGC	TGG	TCT	CTG	GAC	TAC	1632
Leu	Val	Asp	Cys	Tyr	Ile	Asn	Leu	Gly	Ala	Arg	Trp	Ser	Leu	Asp	Tyr	
	530					535					540					
ATG	GAC	AAC	GTT	AAT	CCC	TTT	AAC	CAC	CAC	CGC	AAT	GCG	GGC	CTC	CGT	1680
Met	Asp	Asn	Val	Asn	Pro	Phe	Asn	His	His	Arg	Asn	Ala	Gly	Leu	Arg	
545					550					555					560	
TAT	CGC	TCC	ATG	TTG	TTG	GGA	AAC	GGC	CGC	TAC	GTG	CCC	TTT	CAC	ATT	1728
Tyr	Arg	Ser	Met	Leu	Leu	Gly	Asn	Gly	Arg	Tyr	Val	Pro	Phe	His	Ile	
				565					570					575		
CAG	GTG	CCC	CAA	AAG	TTT	TTT	GCC	ATT	AAA	AAC	CTC	CTC	CTC	CTG	CCA	1776
Gln	Val	Pro	Gln	Lys	Phe	Phe	Ala	Ile	Lys	Asn	Leu	Leu	Leu	Leu	Pro	
			580					585					590			
GGC	TCA	TAT	ACA	TAT	GAA	TGG	AAC	TTC	AGG	AAG	GAT	GTT	AAC	ATG	GTT	1824
Gly	Ser	Tyr	Thr	Tyr	Glu	Trp	Asn	Phe	Arg	Lys	Asp	Val	Asn	Met	Val	
		595					600					605				
CTG	CAG	AGC	TCT	CTG	GGA	AAC	GAT	CTT	AGA	GTT	GAC	GGG	GCT	AGC	ATT	1872
Leu	Gln	Ser	Ser	Leu	Gly	Asn	Asp	Leu	Arg	Val	Asp	Gly	Ala	Ser	Ile	
	610					615					620					
AAG	TTT	GAC	AGC	ATT	TGT	CTT	TAC	GCC	ACC	TTC	TTC	CCC	ATG	GCC	CAC	1920
Lys	Phe	Asp	Ser	Ile	Cys	Leu	Tyr	Ala	Thr	Phe	Phe	Pro	Met	Ala	His	
625					630					635					640	
AAC	ACG	GCC	TCC	ACG	CTG	GAA	GCC	ATG	CTC	AGA	AAT	GAC	ACC	AAC	GAC	1968
Asn	Thr	Ala	Ser	Thr	Leu	Glu	Ala	Met	Leu	Arg	Asn	Asp	Thr	Asn	Asp	
				645					650					655		
CAG	TCC	TTT	AAT	GAC	TAC	CTT	TCC	GCC	GCC	AAC	ATG	CTA	TAC	CCC	ATA	2016
Gln	Ser	Phe	Asn	Asp	Tyr	Leu	Ser	Ala	Ala	Asn	Met	Leu	Tyr	Pro	Ile	
			660					665					670			
CCC	GCC	AAC	GCC	ACC	AAC	GTG	CCC	ATC	TCC	ATC	CCA	TCG	CGC	AAC	TGG	2064
Pro	Ala	Asn	Ala	Thr	Asn	Val	Pro	Ile	Ser	Ile	Pro	Ser	Arg	Asn	Trp	
		675					680					685				

GCA GCA TTT CGC GGT TGG GCC TTC ACA CGC TTG AAG ACA AAG GAA ACC Ala Ala Phe Arg Gly Trp Ala Phe Thr Arg Leu Lys Thr Lys Glu Thr 690 695 700	2112
CCT TCC CTG GGA TCA GGC TAC GAC CCT TAC TAC ACC TAC TCT GGC TCC Pro Ser Leu Gly Ser Gly Tyr Asp Pro Tyr Tyr Thr Tyr Ser Gly Ser 705 710 715 720	2160
ATA CCA TAC CTT GAC GGA ACC TTC TAT CTT AAT CAC ACC TTT AAG AAG Ile Pro Tyr Leu Asp Gly Thr Phe Tyr Leu Asn His Thr Phe Lys Lys 725 730 735	2208
GTG GCC ATT ACC TTT GAC TCT TCT GTT AGC TGG CCG GGC AAC GAC CGC Val Ala Ile Thr Phe Asp Ser Ser Val Ser Trp Pro Gly Asn Asp Arg 740 745 750	2256
CTG CTT ACT CCC AAT GAG TTT GAG ATT AAA CGC TCA GTT GAC GGG GAG Leu Leu Thr Pro Asn Glu Phe Glu Ile Lys Arg Ser Val Asp Gly Glu 755 760 765	2304
GGC TAC AAC GTA GCT CAG TGC AAC ATG ACC AAG GAC TGG TTC CTG GTG Gly Tyr Asn Val Ala Gln Cys Asn Met Thr Lys Asp Trp Phe Leu Val 770 775 780	2352
CAG ATG TTG GCC AAC TAC AAT ATT GGC TAC CAG GGC TTC TAC ATT CCA Gln Met Leu Ala Asn Tyr Asn Ile Gly Tyr Gln Gly Phe Tyr Ile Pro 785 790 795 800	2400
GAA AGC TAC AAG GAC CGC ATG TAC TCG TTC TTC AGA AAC TTC CAG CCC Glu Ser Tyr Lys Asp Arg Met Tyr Ser Phe Phe Arg Asn Phe Gln Pro 805 810 815	2448
ATG AGC CGG CAA GTG GTT GAC GAT ACT AAA TAC AAG GAG TAT CAG CAG Met Ser Arg Gln Val Val Asp Asp Thr Lys Tyr Lys Glu Tyr Gln Gln 820 825 830	2496
GTT GGA ATT CTT CAC CAG CAT AAC AAC TCA GGA TTC GTA GGC TAC CTC Val Gly Ile Leu His Gln His Asn Asn Ser Gly Phe Val Gly Tyr Leu 835 840 845	2544
GCT CCC ACC ATG CGC GAG GGA CAG GCT TAC CCC GCC AAC GTG CCC TAC Ala Pro Thr Met Arg Glu Gly Gln Ala Tyr Pro Ala Asn Val Pro Tyr 850 855 860	2592
CCA CTA ATA GGC AAA ACC GCG GTT GAC AGT ATT ACC CAG AAA AAG TTT Pro Leu Ile Gly Lys Thr Ala Val Asp Ser Ile Thr Gln Lys Lys Phe 865 870 875 880	2640
CTT TGC GAT CGC ACC CTT TGG CGC ATC CCA TTC TCC AGT AAC TTT ATG Leu Cys Asp Arg Thr Leu Trp Arg Ile Pro Phe Ser Ser Asn Phe Met 885 890 895	2688
TCC ATG GGC GCA CTC ACA GAC CTG GGC CAA AAC CTT CTC TAC GCC AAC Ser Met Gly Ala Leu Thr Asp Leu Gly Gln Asn Leu Leu Tyr Ala Asn 900 905 910	2736
TCC GCC CAC GCG CTA GAC ATG ACT TTT GAG GTG GAT CCC ATG GAC GAG Ser Ala His Ala Leu Asp Met Thr Phe Glu Val Asp Pro Met Asp Glu 915 920 925	2784
CCC ACC CTT CTT TAT GTT TTG TTT GAA GTC TTT GAC GTG GTC CGT GTG Pro Thr Leu Leu Tyr Val Leu Phe Glu Val Phe Asp Val Val Arg Val 930 935 940	2832

CAC CAG CCG CAC CGC GGC GTC ATC GAG ACC GTG TAC CTG CGC ACG CCC 2880  
 His Gln Pro His Arg Gly Val Ile Glu Thr Val Tyr Leu Arg Thr Pro  
 945 950 955 960

TTC TCG GCC GGC AAC GCC ACA ACA TAA 2907  
 Phe Ser Ala Gly Asn Ala Thr Thr  
 965

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 968 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Met Ala Thr Pro Ser Met Met Pro Gln Trp Ser Tyr Met His Ile Ser  
 1 5 10 15  
 Gly Gln Asp Ala Ser Glu Tyr Leu Ser Pro Gly Leu Val Gln Phe Ala  
 20 25 30  
 Arg Ala Thr Glu Thr Tyr Phe Ser Leu Asn Asn Lys Phe Arg Asn Pro  
 35 40 45  
 Thr Val Ala Pro Thr His Asp Val Thr Thr Asp Arg Ser Gln Arg Leu  
 50 55 60  
 Thr Leu Arg Phe Ile Pro Val Asp Arg Glu Asp Thr Ala Tyr Ser Tyr  
 65 70 75 80  
 Lys Ala Arg Phe Thr Leu Ala Val Gly Asp Asn Arg Val Leu Asp Met  
 85 90 95  
 Ala Ser Thr Tyr Phe Asp Ile Arg Gly Val Leu Asp Arg Gly Pro Thr  
 100 105 110  
 Phe Lys Pro Tyr Ser Gly Thr Ala Tyr Asn Ala Leu Ala Pro Lys Gly  
 115 120 125  
 Ala Pro Asn Ser Cys Glu Trp Glu Gln Thr Glu Asp Ser Gly Arg Ala  
 130 135 140  
 Val Ala Glu Asp Glu Glu Glu Asp Glu Asp Glu Glu Glu Glu  
 145 150 155 160  
 Glu Glu Gln Asn Ala Arg Asp Gln Ala Thr Lys Lys Thr His Val Tyr  
 165 170 175  
 Ala Gln Ala Pro Leu Ser Gly Glu Thr Ile Thr Lys Ser Gly Leu Gln  
 180 185 190  
 Ile Gly Ser Asp Asn Ala Glu Thr Gln Ala Lys Pro Val Tyr Ala Asp  
 195 200 205  
 Pro Ser Tyr Gln Pro Glu Pro Gln Ile Gly Glu Ser Gln Trp Asn Glu  
 210 215 220  
 Ala Asp Ala Asn Ala Ala Gly Gly Arg Val Leu Lys Lys Thr Thr Pro  
 225 230 235 240

Met Lys Pro Cys Tyr Gly Ser Tyr Ala Arg Pro Thr Asn Pro Phe Gly  
 245 250 255  
 Gly Gln Ser Val Leu Val Pro Asp Glu Lys Gly Val Pro Leu Pro Lys  
 260 265 270  
 Val Asp Leu Gln Phe Phe Ser Asn Thr Thr Ser Leu Asn Asp Arg Gln  
 275 280 285  
 Gly Asn Ala Thr Lys Pro Lys Val Val Leu Tyr Ser Glu Asp Val Asn  
 290 295 300  
 Met Glu Thr Pro Asp Thr His Leu Ser Tyr Lys Pro Gly Lys Gly Asp  
 305 310 315 320  
 Glu Asn Ser Lys Ala Met Leu Gly Gln Gln Ser Met Pro Asn Arg Pro  
 325 330 335  
 Asn Tyr Ile Ala Phe Arg Asp Asn Phe Ile Gly Leu Met Tyr Tyr Asn  
 340 345 350  
 Ser Thr Gly Asn Met Gly Val Leu Ala Gly Gln Ala Ser Gln Leu Asn  
 355 360 365  
 Ala Val Val Asp Leu Gln Asp Arg Asn Thr Glu Leu Ser Tyr Gln Leu  
 370 375 380  
 Leu Leu Asp Ser Ile Gly Asp Arg Thr Arg Tyr Phe Ser Met Trp Asn  
 385 390 395 400  
 Gln Ala Val Asp Ser Tyr Asp Pro Asp Val Arg Ile Ile Glu Asn His  
 405 410 415  
 Gly Thr Glu Asp Glu Leu Pro Asn Tyr Cys Phe Pro Leu Gly Gly Ile  
 420 425 430  
 Gly Val Thr Asp Thr Tyr Gln Ala Ile Lys Ala Asn Gly Asn Gly Ser  
 435 440 445  
 Gly Asp Asn Gly Asp Thr Thr Trp Thr Lys Asp Glu Thr Phe Ala Thr  
 450 455 460  
 Arg Asn Glu Ile Gly Val Gly Asn Asn Phe Ala Met Glu Ile Asn Leu  
 465 470 475 480  
 Asn Ala Asn Leu Trp Arg Asn Phe Leu Tyr Ser Asn Ile Ala Leu Tyr  
 485 490 495  
 Leu Pro Asp Lys Leu Lys Tyr Asn Pro Thr Asn Val Glu Ile Ser Asp  
 500 505 510  
 Asn Pro Asn Thr Tyr Asp Tyr Met Asn Lys Arg Val Val Ala Pro Gly  
 515 520 525  
 Leu Val Asp Cys Tyr Ile Asn Leu Gly Ala Arg Trp Ser Leu Asp Tyr  
 530 535 540  
 Met Asp Asn Val Asn Pro Phe Asn His His Arg Asn Ala Gly Leu Arg  
 545 550 555 560  
 Tyr Arg Ser Met Leu Leu Gly Asn Gly Arg Tyr Val Pro Phe His Ile  
 565 570 575

65

Gln Val Pro Gln Lys Phe Phe Ala Ile Lys Asn Leu Leu Leu Leu Pro  
 580 585 590  
 Gly Ser Tyr Thr Tyr Glu Trp Asn Phe Arg Lys Asp Val Asn Met Val  
 595 600 605  
 Leu Gln Ser Ser Leu Gly Asn Asp Leu Arg Val Asp Gly Ala Ser Ile  
 610 615 620  
 Lys Phe Asp Ser Ile Cys Leu Tyr Ala Thr Phe Phe Pro Met Ala His  
 625 630 635 640  
 Asn Thr Ala Ser Thr Leu Glu Ala Met Leu Arg Asn Asp Thr Asn Asp  
 645 650 655  
 Gln Ser Phe Asn Asp Tyr Leu Ser Ala Ala Asn Met Leu Tyr Pro Ile  
 660 665 670  
 Pro Ala Asn Ala Thr Asn Val Pro Ile Ser Ile Pro Ser Arg Asn Trp  
 675 680 685  
 Ala Ala Phe Arg Gly Trp Ala Phe Thr Arg Leu Lys Thr Lys Glu Thr  
 690 695 700  
 Pro Ser Leu Gly Ser Gly Tyr Asp Pro Tyr Tyr Thr Tyr Ser Gly Ser  
 705 710 715 720  
 Ile Pro Tyr Leu Asp Gly Thr Phe Tyr Leu Asn His Thr Phe Lys Lys  
 725 730 735  
 Val Ala Ile Thr Phe Asp Ser Ser Val Ser Trp Pro Gly Asn Asp Arg  
 740 745 750  
 Leu Leu Thr Pro Asn Glu Phe Glu Ile Lys Arg Ser Val Asp Gly Glu  
 755 760 765  
 Gly Tyr Asn Val Ala Gln Cys Asn Met Thr Lys Asp Trp Phe Leu Val  
 770 775 780  
 Gln Met Leu Ala Asn Tyr Asn Ile Gly Tyr Gln Gly Phe Tyr Ile Pro  
 785 790 795 800  
 Glu Ser Tyr Lys Asp Arg Met Tyr Ser Phe Phe Arg Asn Phe Gln Pro  
 805 810 815  
 Met Ser Arg Gln Val Val Asp Asp Thr Lys Tyr Lys Glu Tyr Gln Gln  
 820 825 830  
 Val Gly Ile Leu His Gln His Asn Asn Ser Gly Phe Val Gly Tyr Leu  
 835 840 845  
 Ala Pro Thr Met Arg Glu Gly Gln Ala Tyr Pro Ala Asn Val Pro Tyr  
 850 855 860  
 Pro Leu Ile Gly Lys Thr Ala Val Asp Ser Ile Thr Gln Lys Lys Phe  
 865 870 875 880  
 Leu Cys Asp Arg Thr Leu Trp Arg Ile Pro Phe Ser Ser Asn Phe Met  
 885 890 895  
 Ser Met Gly Ala Leu Thr Asp Leu Gly Gln Asn Leu Leu Tyr Ala Asn  
 900 905 910

66

Ser Ala His Ala Leu Asp Met Thr Phe Glu Val Asp Pro Met Asp Glu  
 915 920 925

Pro Thr Leu Leu Tyr Val Leu Phe Glu Val Phe Asp Val Val Arg Val  
 930 935 940

His Gln Pro His Arg Gly Val Ile Glu Thr Val Tyr Leu Arg Thr Pro  
 945 950 955 960

Phe Ser Ala Gly Asn Ala Thr Thr

## (2) INFORMATION FOR SEQ ID NO:3:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2858 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: DNA (genomic)

## (ix) FEATURE

- (A) NAME/KEY: misc\_feature
- (B) LOCATION: 951, 952
- (D) OTHER INFORMATION: /note="Xaa can be either Gln, His, or

Thr"

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

ATG GCT ACC CCT TCG ATG ATG CCG CAG TGG TCT TAC ATG CAC ATC TCG	48
Met Ala Thr Pro Ser Met Met Pro Gln Trp Ser Tyr Met His Ile Ser	
1 5 10 15	
GGC CAG GAC GCC TCG GAG TAC CTG AGC CCC GGG CTG GTG CAG TTT GCC	96
Gly Gln Asp Ala Ser Glu Tyr Leu Ser Pro Gly Leu Val Gln Phe Ala	
20 25 30	
CGC GCC ACC GAG ACG TAC TTC AGC CTG AAT AAC AAG TTT AGA AAC CCC	144
Arg Ala Thr Glu Thr Tyr Phe Ser Leu Asn Asn Lys Phe Arg Asn Pro	
35 40 45	
ACG GTG GCG CCT ACG CAC GAC GTG ACC ACA GAC CGG TCC CAG CGT TTG	192
Thr Val Ala Pro Thr His Asp Val Thr Thr Asp Arg Ser Gln Arg Leu	
50 55 60	
ACG CTG CGG TTC ATC CCT GTG GAC CGT GAG GAT ACT GCG TAC TCG TAC	240
Thr Leu Arg Phe Ile Pro Val Asp Arg Glu Asp Thr Ala Tyr Ser Tyr	
65 70 75 80	
AAG GCG CGG TTC ACC CTA GCT GTG GGT GAT AAC CGT GTG CTG GAC ATG	288
Lys Ala Arg Phe Thr Leu Ala Val Gly Asp Asn Arg Val Leu Asp Met	
85 90 95	
GCT TCC ACG TAC TTT GAC ATC CGC GGC GTG CTG GAC AGG GGC CCT ACT	336
Ala Ser Thr Tyr Phe Asp Ile Arg Gly Val Leu Asp Arg Gly Pro Thr	
100 105 110	
TTT AAG CCC TAC TCT GGC ACT GCC TAC AAC GCC CTG GCT CCC AAG GGT	384
Phe Lys Pro Tyr Ser Gly Thr Ala Tyr Asn Ala Leu Ala Pro Lys Gly	
115 120 125	
GCC CCA AAT CCT TGC GAA TGG GAT GAA GCT GCT ACT GCT CTT GAA ATA	432
Ala Pro Asn Pro Cys Glu Trp Asp Glu Ala Ala Thr Ala Leu Glu Ile	
130 135 140	

67

AAC CTA GAA GAA GAG GAC GAT GAC AAC GAA GAC GAA GTA GAC GAG CAA Asn Leu Glu Glu Glu Asp Asp Asp Asn Glu Asp Glu Val Asp Glu Gln 145 150 155 160	480
GCT GAG CAG CAA AAA ACT CAC GTA TTT GGG CAG GCG CCT TAT TCT GGT Ala Glu Gln Gln Lys Thr His Val Phe Gly Gln Ala Pro Tyr Ser Gly 165 170 175	528
ATA AAT ATT ACA AAG GAG GGT ATT CAA ATA GGT GTC GAA GGT CAA ACA Ile Asn Ile Thr Lys Glu Gly Ile Gln Ile Gly Val Glu Gly Gln Thr 180 185 190	576
CCT AAA TAT GCC GAT AAA ACA TTT CAA CCT GAA CCT CAA ATA GGA GAA Pro Lys Tyr Ala Asp Lys Thr Phe Gln Pro Glu Pro Gln Ile Gly Glu 195 200 205	624
TCT CAG TGG TAC GAA ACT GAA ATT AAT CAT GCA GCT GGG AGA GTC CTT Ser Gln Trp Tyr Glu Thr Glu Ile Asn His Ala Ala Gly Arg Val Leu 210 215 220	672
AAA AAG ACT ACC CCA ATG AAA CCA TGT TAC GGT TCA TAT GCA AAA CCC Lys Lys Thr Thr Pro Met Lys Pro Cys Tyr Gly Ser Tyr Ala Lys Pro 225 230 235 240	720
ACA AAT GAA AAT GGA GGG CAA GGC ATT CTT GTA AAG CAA CAA AAT GGA Thr Asn Glu Asn Gly Gly Gln Gly Ile Leu Val Lys Gln Gln Asn Gly 245 250 255	768
AAG CTA GAA AGT CAA GTG GAA ATG CAA TTT TTC TCA ACT ACT GAG GCG Lys Leu Glu Ser Gln Val Glu Met Gln Phe Phe Ser Thr Thr Glu Ala 260 265 270	816
ACC GCA GGC AAT GGT GAT AAC TTG ACT CCT AAA GTG GTA TTG TAC AGT Thr Ala Gly Asn Gly Asp Asn Leu Thr Pro Lys Val Val Leu Tyr Ser 275 280 285	864
GAA GAT GTA GAT ATA GAA ACC CCA GAC ACT CAT ATT TCT TAC ATG CCC Glu Asp Val Asp Ile Glu Thr Pro Asp Thr His Ile Ser Tyr Met Pro 290 295 300	912
ACT ATT AAG GAA GGT AAC TCA CGA GAA CTA ATG GGC CAA CAA TCT ATG Thr Ile Lys Glu Gly Asn Ser Arg Glu Leu Met Gly Gln Gln Ser Met 305 310 315 320	960
CCC AAC AGG CCT AAT TAC ATT GCT TTT AGG GAC AAT TTT ATT GGT CTA Pro Asn Arg Pro Asn Tyr Ile Ala Phe Arg Asp Asn Phe Ile Gly Leu 325 330 335	1008
ATG TAT TAC AAC AGC ACG GGT AAT ATG GGT GTT CTG GCG GGC CAA GCA Met Tyr Tyr Asn Ser Thr Gly Asn Met Gly Val Leu Ala Gly Gln Ala 340 345 350	1056
TCG CAG TTG AAT GCT GTT GTA GAT TTG CAA GAC AGA AAC ACA GAG CTT Ser Gln Leu Asn Ala Val Val Asp Leu Gln Asp Arg Asn Thr Glu Leu 355 360 365	1104
TCA TAC CAG CTT TTG CTT GAT TCC ATT GGT GAT AGA ACC AGG TAC TTT Ser Tyr Gln Leu Leu Leu Asp Ser Ile Gly Asp Arg Thr Arg Tyr Phe 370 375 380	1152
TCT ATG TGG AAT CAG GCT GTT GAC AGC TAT GAT CCA GAT GTT AGA ATT Ser Met Trp Asn Gln Ala Val Asp Ser Tyr Asp Pro Asp Val Arg Ile 385 390 395 400	1200

68

ATT GAA AAT CAT GGA ACT GAA GAT GAA CTT CCA AAT TAC TGC TTT CCA Ile Glu Asn His Gly Thr Glu Asp Glu Leu Pro Asn Tyr Cys Phe Pro 405 410 415	1248
CTG GGA GGT GTG ATT AAT ACA GAG ACT CTT ACC AAG GTA AAA CCT AAA Leu Gly Gly Val Ile Asn Thr Glu Thr Leu Thr Lys Val Lys Pro Lys 420 425 430	1296
ACA GGT CAG GAA AAT GGA TGG GAA AAA GAT GCT ACA GAA TTT TCA GAT Thr Gly Gln Glu Asn Gly Trp Glu Lys Asp Ala Thr Glu Phe Ser Asp 435 440 445	1344
AAA AAT GAA ATA AGA GTT GGA AAT AAT TTT GCC ATG GAA ATC AAT CTA Lys Asn Glu Ile Arg Val Gly Asn Asn Phe Ala Met Glu Ile Asn Leu 450 455 460	1392
AAT GCC AAC CTG TGG AGA AAT TTC CTG TAC TCC AAC ATA GCG CTG TAT Asn Ala Asn Leu Trp Arg Asn Phe Leu Tyr Ser Asn Ile Ala Leu Tyr 465 470 475 480	1440
TTG CCC GAC AAG CTA AAG TAC AGT CCT TCC AAC GTA AAA ATT TCT GAT Leu Pro Asp Lys Leu Lys Tyr Ser Pro Ser Asn Val Lys Ile Ser Asp 485 490 495	1488
AAC CCA AAC ACC TAC GAC TAC ATG AAC AAG CGA GTG GTG GCT CCC GGG Asn Pro Asn Thr Tyr Asp Tyr Met Asn Lys Arg Val Val Ala Pro Gly 500 505 510	1536
TTA GTG GAC TGC TAC ATT AAC CTT GGA GCA CGC TGG TCC CTT GAC TAT Leu Val Asp Cys Tyr Ile Asn Leu Gly Ala Arg Trp Ser Leu Asp Tyr 515 520 525	1584
ATG GAC AAC GTC AAC CCA TTT AAC CAC CAC CGC AAT GCT GGC CTG CGC Met Asp Asn Val Asn Pro Phe Asn His His Arg Asn Ala Gly Leu Arg 530 535 540	1632
TAC CGC TCA ATG TTG CTG GGC AAT GGT CGC TAT GTG CCC TTC CAC ATC Tyr Arg Ser Met Leu Leu Gly Asn Gly Arg Tyr Val Pro Phe His Ile 545 550 555 560	1680
CAG GTG CCT CAG AAG TTC TTT GCC ATT AAA AAC CTC CTT CTC CTG CCG Gln Val Pro Gln Lys Phe Phe Ala Ile Lys Asn Leu Leu Leu Leu Pro 565 570 575	1728
GGC TCA TAC ACC TAC GAG TGG AAC TTC AGG AAG GAT GTT AAC ATG GTT Gly Ser Tyr Thr Tyr Glu Trp Asn Phe Arg Lys Asp Val Asn Met Val 580 585 590	1776
CTG CAG AGC TCC CTA GGA AAT GAC CTA AGG GTT GAC GGA GCC AGC ATT Leu Gln Ser Ser Leu Gly Asn Asp Leu Arg Val Asp Gly Ala Ser Ile 595 600 605	1824
AAG TTT GAT AGC ATT TGC CTT TAC GCC ACC TTC TTC CCC ATG GCC CAC Lys Phe Asp Ser Ile Cys Leu Tyr Ala Thr Phe Phe Pro Met Ala His 610 615 620	1872
AAC ACC GCC TCC ACG CTT GAG GCC ATG CTT AGA AAC GAC ACC AAC GAC Asn Thr Ala Ser Thr Leu Glu Ala Met Leu Arg Asn Asp Thr Asn Asp 625 630 635 640	1920
CAG TCC TTT AAC GAC TAT CTC TCC GCC GCC AAC ATG CTC TAC CCT ATA Gln Ser Phe Asn Asp Tyr Leu Ser Ala Ala Asn Met Leu Tyr Pro Ile 645 650 655	1968

CCC	GCC	AAC	GCT	ACC	AAC	GTG	CCC	ATA	TCC	ATC	CCC	TCC	CGC	AAC	TGG	2016
Pro	Ala	Asn	Ala	Thr	Asn	Val	Pro	Ile	Ser	Ile	Pro	Ser	Arg	Asn	Trp	
			660					665					670			
GCG	GCT	TTC	CGC	GGC	TGG	GCC	TTC	ACG	CGC	CTT	AAG	ACT	AAG	GAA	ACC	2064
Ala	Ala	Phe	Arg	Gly	Trp	Ala	Phe	Thr	Arg	Leu	Lys	Thr	Lys	Glu	Thr	
		675					680					685				
CCA	TCA	CTG	GGC	TCG	GGC	TAC	GAC	CCT	TAT	TAC	ACC	TAC	TCT	GGC	TCT	2112
Pro	Ser	Leu	Gly	Ser	Gly	Tyr	Asp	Pro	Tyr	Tyr	Thr	Tyr	Ser	Gly	Ser	
	690					695					700					
ATA	CCC	TAC	CTA	GAT	GGA	ACC	TTT	TAC	CTC	AAC	CAC	ACC	TTT	AAG	AAG	2160
Ile	Pro	Tyr	Leu	Asp	Gly	Thr	Phe	Tyr	Leu	Asn	His	Thr	Phe	Lys	Lys	
705					710				715						720	
GTG	GCC	ATT	ACC	TTT	GAC	TCT	TCT	GTC	AGC	TGG	CCT	GGC	AAT	GAC	CGC	2208
Val	Ala	Ile	Thr	Phe	Asp	Ser	Ser	Val	Ser	Trp	Pro	Gly	Asn	Asp	Arg	
				725					730					735		
CTG	CTT	ACC	CCC	AAC	GAG	TTT	GAA	ATT	AAG	CGC	TCA	GTT	GAC	GGG	GAG	2256
Leu	Leu	Thr	Pro	Asn	Glu	Phe	Glu	Ile	Lys	Arg	Ser	Val	Asp	Gly	Glu	
			740					745					750			
GGT	TAC	AAC	GTT	GCC	CAG	TGT	AAC	ATG	ACC	AAA	GAC	TGG	TTC	CTG	GTA	2304
Gly	Tyr	Asn	Val	Ala	Gln	Cys	Asn	Met	Thr	Lys	Asp	Trp	Phe	Leu	Val	
		755					760					765				
CAA	ATG	CTA	GCT	AAC	TAC	AAC	ATT	GGC	TAC	CAG	GGC	TTC	TAT	ATC	CCA	2352
Gln	Met	Leu	Ala	Asn	Tyr	Asn	Ile	Gly	Tyr	Gln	Gly	Phe	Tyr	Ile	Pro	
	770					775					780					
GAG	AGC	TAC	AAG	GAC	CGC	ATG	TAC	TCC	TTC	TTT	AGA	AAC	TTC	CAG	CCC	2400
Glu	Ser	Tyr	Lys	Asp	Arg	Met	Tyr	Ser	Phe	Phe	Arg	Asn	Phe	Gln	Pro	
785					790					795					800	
ATG	AGC	CGT	CAG	GTG	GTG	GAT	GAT	ACT	AAA	TAC	AAG	GAC	TAC	CAA	CAG	2448
Met	Ser	Arg	Gln	Val	Val	Asp	Asp	Thr	Lys	Tyr	Lys	Asp	Tyr	Gln	Gln	
			805						810					815		
GTG	GGC	ATC	CTA	CAC	CAA	CAC	AAC	AAC	TCT	GGA	TTT	GTT	GGC	TAC	CTT	2496
Val	Gly	Ile	Leu	His	Gln	His	Asn	Asn	Ser	Gly	Phe	Val	Gly	Tyr	Leu	
			820					825					830			
GCC	CCC	ACC	ATG	CGC	GAA	GGA	CAG	GCC	TAC	CCT	GCT	AAC	TTC	CCC	TAT	2544
Ala	Pro	Thr	Met	Arg	Glu	Gly	Gln	Ala	Tyr	Pro	Ala	Asn	Phe	Pro	Tyr	
		835					840					845				
CCG	CTT	ATA	GGC	AAG	ACC	GCA	GTT	GAC	AGC	ATT	ACC	CAG	AAA	AAG	TTT	2592
Pro	Leu	Ile	Gly	Lys	Thr	Ala	Val	Asp	Ser	Ile	Thr	Gln	Lys	Lys	Phe	
	850					855					860					
CTT	TGC	GAT	CGC	ACC	CTT	TGG	CGC	ATC	CCA	TTC	TCC	AGT	AAC	TTT	ATG	2640
Leu	Cys	Asp	Arg	Thr	Leu	Trp	Arg	Ile	Pro	Phe	Ser	Ser	Asn	Phe	Met	
865					870				875						880	
TCC	ATG	GGC	GCA	CTC	ACA	GAC	CTG	GGC	CAA	AAC	CTT	CTC	TAC	GCC	AAC	2688
Ser	Met	Gly	Ala	Leu	Thr	Asp	Leu	Gly	Gln	Asn	Leu	Leu	Tyr	Ala	Asn	
			885					890						895		
TCC	GCC	CAC	GCG	CTA	GAC	ATG	ACT	TTT	GAG	GTG	GAT	CCC	ATG	GAC	GAG	2736
Ser	Ala	His	Ala	Leu	Asp	Met	Thr	Phe	Glu	Val	Asp	Pro	Met	Asp	Glu	
			900					905					910			

70

CCC ACC CTT CTT TAT GTT TTG TTT GAA GTC TTT GAC GTG GTC CGT GTG 2784  
 Pro Thr Leu Leu Tyr Val Leu Phe Glu Val Phe Asp Val Val Arg Val  
 915 920 925  
 CAC CGG CCG CAC CGC GGC GTC ATC GAA ACC GTG TAC CTG CGC ACG CCC 2832  
 His Arg Pro His Arg Gly Val Ile Glu Thr Val Tyr Leu Arg Thr Pro  
 930 935 940  
 TTC TCG GCC GGC AAC GCA HHH HHH HH 2858  
 Phe Ser Ala Gly Asn Ala Xaa Xaa  
 945 950

## (2) INFORMATION FOR SEQ ID NO:4:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 952 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (ix) FEATURE

- (A) NAME/KEY: misc feature  
 (B) LOCATION: 951,952  
 (D) OTHER INFORMATION: /note= "Xaa can be either Gln, His, or

Thr"

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Met Ala Thr Pro Ser Met Met Pro Gln Trp Ser Tyr Met His Ile Ser  
 1 5 10 15  
 Gly Gln Asp Ala Ser Glu Tyr Leu Ser Pro Gly Leu Val Gln Phe Ala  
 20 25 30  
 Arg Ala Thr Glu Thr Tyr Phe Ser Leu Asn Asn Lys Phe Arg Asn Pro  
 35 40 45  
 Thr Val Ala Pro Thr His Asp Val Thr Thr Asp Arg Ser Gln Arg Leu  
 50 55 60  
 Thr Leu Arg Phe Ile Pro Val Asp Arg Glu Asp Thr Ala Tyr Ser Tyr  
 65 70 75 80  
 Lys Ala Arg Phe Thr Leu Ala Val Gly Asp Asn Arg Val Leu Asp Met  
 85 90 95  
 Ala Ser Thr Tyr Phe Asp Ile Arg Gly Val Leu Asp Arg Gly Pro Thr  
 100 105 110  
 Phe Lys Pro Tyr Ser Gly Thr Ala Tyr Asn Ala Leu Ala Pro Lys Gly  
 115 120 125  
 Ala Pro Asn Pro Cys Glu Trp Asp Glu Ala Ala Thr Ala Leu Glu Ile  
 130 135 140  
 Asn Leu Glu Glu Glu Asp Asp Asp Asn Glu Asp Glu Val Asp Glu Gln  
 145 150 155 160  
 Ala Glu Gln Gln Lys Thr His Val Phe Gly Gln Ala Pro Tyr Ser Gly  
 165 170 175  
 Ile Asn Ile Thr Lys Glu Gly Ile Gln Ile Gly Val Glu Gly Gln Thr  
 180 185 190

Pro Lys Tyr Ala Asp Lys Thr Phe Gln Pro Glu Pro Gln Ile Gly Glu  
 195 200 205  
 Ser Gln Trp Tyr Glu Thr Glu Ile Asn His Ala Ala Gly Arg Val Leu  
 210 215 220  
 Lys Lys Thr Thr Pro Met Lys Pro Cys Tyr Gly Ser Tyr Ala Lys Pro  
 225 230 235 240  
 Thr Asn Glu Asn Gly Gly Gln Gly Ile Leu Val Lys Gln Gln Asn Gly  
 245 250 255  
 Lys Leu Glu Ser Gln Val Glu Met Gln Phe Phe Ser Thr Thr Glu Ala  
 260 265 270  
 Thr Ala Gly Asn Gly Asp Asn Leu Thr Pro Lys Val Val Leu Tyr Ser  
 275 280 285  
 Glu Asp Val Asp Ile Glu Thr Pro Asp Thr His Ile Ser Tyr Met Pro  
 290 295 300  
 Thr Ile Lys Glu Gly Asn Ser Arg Glu Leu Met Gly Gln Gln Ser Met  
 305 310 315 320  
 Pro Asn Arg Pro Asn Tyr Ile Ala Phe Arg Asp Asn Phe Ile Gly Leu  
 325 330 335  
 Met Tyr Tyr Asn Ser Thr Gly Asn Met Gly Val Leu Ala Gly Gln Ala  
 340 345 350  
 Ser Gln Leu Asn Ala Val Val Asp Leu Gln Asp Arg Asn Thr Glu Leu  
 355 360 365  
 Ser Tyr Gln Leu Leu Leu Asp Ser Ile Gly Asp Arg Thr Arg Tyr Phe  
 370 375 380  
 Ser Met Trp Asn Gln Ala Val Asp Ser Tyr Asp Pro Asp Val Arg Ile  
 385 390 395 400  
 Ile Glu Asn His Gly Thr Glu Asp Glu Leu Pro Asn Tyr Cys Phe Pro  
 405 410 415  
 Leu Gly Gly Val Ile Asn Thr Glu Thr Leu Thr Lys Val Lys Pro Lys  
 420 425 430  
 Thr Gly Gln Glu Asn Gly Trp Glu Lys Asp Ala Thr Glu Phe Ser Asp  
 435 440 445  
 Lys Asn Glu Ile Arg Val Gly Asn Asn Phe Ala Met Glu Ile Asn Leu  
 450 455 460  
 Asn Ala Asn Leu Trp Arg Asn Phe Leu Tyr Ser Asn Ile Ala Leu Tyr  
 465 470 475 480  
 Leu Pro Asp Lys Leu Lys Tyr Ser Pro Ser Asn Val Lys Ile Ser Asp  
 485 490 495  
 Asn Pro Asn Thr Tyr Asp Tyr Met Asn Lys Arg Val Val Ala Pro Gly  
 500 505 510  
 Leu Val Asp Cys Tyr Ile Asn Leu Gly Ala Arg Trp Ser Leu Asp Tyr  
 515 520 525

Met Asp Asn Val Asn Pro Phe Asn His His Arg Asn Ala Gly Leu Arg  
 530 535 540  
 Tyr Arg Ser Met Leu Leu Gly Asn Gly Arg Tyr Val Pro Phe His Ile  
 545 550 555 560  
 Gln Val Pro Gln Lys Phe Phe Ala Ile Lys Asn Leu Leu Leu Leu Pro  
 565 570 575  
 Gly Ser Tyr Thr Tyr Glu Trp Asn Phe Arg Lys Asp Val Asn Met Val  
 580 585 590  
 Leu Gln Ser Ser Leu Gly Asn Asp Leu Arg Val Asp Gly Ala Ser Ile  
 595 600 605  
 Lys Phe Asp Ser Ile Cys Leu Tyr Ala Thr Phe Phe Pro Met Ala His  
 610 615 620  
 Asn Thr Ala Ser Thr Leu Glu Ala Met Leu Arg Asn Asp Thr Asn Asp  
 625 630 635 640  
 Gln Ser Phe Asn Asp Tyr Leu Ser Ala Ala Asn Met Leu Tyr Pro Ile  
 645 650 655  
 Pro Ala Asn Ala Thr Asn Val Pro Ile Ser Ile Pro Ser Arg Asn Trp  
 660 665 670  
 Ala Ala Phe Arg Gly Trp Ala Phe Thr Arg Leu Lys Thr Lys Glu Thr  
 675 680 685  
 Pro Ser Leu Gly Ser Gly Tyr Asp Pro Tyr Tyr Thr Tyr Ser Gly Ser  
 690 695 700  
 Ile Pro Tyr Leu Asp Gly Thr Phe Tyr Leu Asn His Thr Phe Lys Lys  
 705 710 715 720  
 Val Ala Ile Thr Phe Asp Ser Ser Val Ser Trp Pro Gly Asn Asp Arg  
 725 730 735  
 Leu Leu Thr Pro Asn Glu Phe Glu Ile Lys Arg Ser Val Asp Gly Glu  
 740 745 750  
 Gly Tyr Asn Val Ala Gln Cys Asn Met Thr Lys Asp Trp Phe Leu Val  
 755 760 765  
 Gln Met Leu Ala Asn Tyr Asn Ile Gly Tyr Gln Gly Phe Tyr Ile Pro  
 770 775 780  
 Glu Ser Tyr Lys Asp Arg Met Tyr Ser Phe Phe Arg Asn Phe Gln Pro  
 785 790 795 800  
 Met Ser Arg Gln Val Val Asp Asp Thr Lys Tyr Lys Asp Tyr Gln Gln  
 805 810 815  
 Val Gly Ile Leu His Gln His Asn Asn Ser Gly Phe Val Gly Tyr Leu  
 820 825 830  
 Ala Pro Thr Met Arg Glu Gly Gln Ala Tyr Pro Ala Asn Phe Pro Tyr  
 835 840 845  
 Pro Leu Ile Gly Lys Thr Ala Val Asp Ser Ile Thr Gln Lys Lys Phe  
 850 855 860

73

Leu Cys Asp Arg Thr Leu Trp Arg Ile Pro Phe Ser Ser Asn Phe Met  
 865 870 875 880  
 Ser Met Gly Ala Leu Thr Asp Leu Gly Gln Asn Leu Leu Tyr Ala Asn  
 885 890 895  
 Ser Ala His Ala Leu Asp Met Thr Phe Glu Val Asp Pro Met Asp Glu  
 900 905 910  
 Pro Thr Leu Leu Tyr Val Leu Phe Glu Val Phe Asp Val Val Arg Val  
 915 920 925  
 His Arg Pro His Arg Gly Val Ile Glu Thr Val Tyr Leu Arg Thr Pro  
 930 935 940  
 Phe Ser Ala Gly Asn Ala Xaa Xaa  
 945 950

## (2) INFORMATION FOR SEQ ID NO:5:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 603 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: double  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: DNA (genomic)

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

TCC TGT GAG TGG GAA CAA ACC GAA GAT AGC GGC CGG GCA GTT GCC GAG	48
Ser Cys Glu Trp Glu Gln Thr Glu Asp Ser Gly Arg Ala Val Ala Glu	
1 5 10 15	
GAT GAA GAA GAG GAA GAT GAA GAT GAA GAA GAG GAA GAA GAA GAG CAA	96
Asp Glu Glu Glu Glu Asp Glu Asp Glu Glu Glu Glu Glu Glu Gln	
20 25 30	
AAC GCT CGA GAT CAG GCT ACT AAG AAA ACA CAT GTC TAT GCC CAG GCT	144
Asn Ala Arg Asp Gln Ala Thr Lys Lys Thr His Val Tyr Ala Gln Ala	
35 40 45	
CCT TTG TCT GGA GAA ACA ATT ACA AAA AGC GGG CTA CAA ATA GGA TCA	192
Pro Leu Ser Gly Glu Thr Ile Thr Lys Ser Gly Leu Gln Ile Gly Ser	
50 55 60	
GAC AAT GCA GAA ACA CAA GCT AAA CCT GTA TAC GCA GAT CCT TCC TAT	240
Asp Asn Ala Glu Thr Gln Ala Lys Pro Val Tyr Ala Asp Pro Ser Tyr	
65 70 75 80	
CAA CCA GAA CCT CAA ATT GGC GAA TCT CAG TGG AAC GAA GCT GAT GCT	288
Gln Pro Glu Pro Gln Ile Gly Glu Ser Gln Trp Asn Glu Ala Asp Ala	
85 90 95	
AAT GCG GCA GGA GGG AGA GTG CTT AAA AAA ACA ACT CCC ATG AAA CCA	336
Asn Ala Ala Gly Gly Arg Val Leu Lys Lys Thr Thr Pro Met Lys Pro	
100 105 110	
TGC TAT GGA TCT TAT GCC AGG CCT ACA AAT CCT TTT GGT GGT CAA TCC	384
Cys Tyr Gly Ser Tyr Ala Arg Pro Thr Asn Pro Phe Gly Gly Gln Ser	
115 120 125	

74

GTT CTG GTT CCG GAT GAA AAA GGG GTG CCT CTT CCA AAG GTT GAC TTG Val Leu Val Pro Asp Glu Lys Gly Val Pro Leu Pro Lys Val Asp Leu 130 135 140	432
CAA TTC TTC TCA AAT ACT ACC TCT TTG AAC GAC CGG CAA GGC AAT GCT Gln Phe Phe Ser Asn Thr Thr Ser Leu Asn Asp Arg Gln Gly Asn Ala 145 150 155 160	480
ACT AAA CCA AAA GTG GTT TTG TAC AGT GAA GAT GTA AAT ATG GAA ACC Thr Lys Pro Lys Val Val Leu Tyr Ser Glu Asp Val Asn Met Glu Thr 165 170 175	528
CCA GAC ACA CAT CTG TCT TAC AAA CCT GGA AAA GGT GAT GAA AAT TCT Pro Asp Thr His Leu Ser Tyr Lys Pro Gly Lys Gly Asp Glu Asn Ser 180 185 190	576
AAA GCT ATG TTG GGT CAA CAA TCT ATG Lys Ala Met Leu Gly Gln Gln Ser Met 195 200	603

## (2) INFORMATION FOR SEQ ID NO:6:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 201 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Ser Cys Glu Trp Glu Gln Thr Glu Asp Ser Gly Arg Ala Val Ala Glu  
1 5 10 15

Asp Glu Glu Glu Glu Asp Glu Asp Glu Glu Glu Glu Glu Glu Gln  
20 25 30

Asn Ala Arg Asp Gln Ala Thr Lys Lys Thr His Val Tyr Ala Gln Ala  
35 40 45

Pro Leu Ser Gly Glu Thr Ile Thr Lys Ser Gly Leu Gln Ile Gly Ser  
50 55 60

Asp Asn Ala Glu Thr Gln Ala Lys Pro Val Tyr Ala Asp Pro Ser Tyr  
65 70 75 80

Gln Pro Glu Pro Gln Ile Gly Glu Ser Gln Trp Asn Glu Ala Asp Ala  
85 90 95

Asn Ala Ala Gly Gly Arg Val Leu Lys Lys Thr Thr Pro Met Lys Pro  
100 105 110

Cys Tyr Gly Ser Tyr Ala Arg Pro Thr Asn Pro Phe Gly Gly Gln Ser  
115 120 125

Val Leu Val Pro Asp Glu Lys Gly Val Pro Leu Pro Lys Val Asp Leu  
130 135 140

Gln Phe Phe Ser Asn Thr Thr Ser Leu Asn Asp Arg Gln Gly Asn Ala  
145 150 155 160

Thr Lys Pro Lys Val Val Leu Tyr Ser Glu Asp Val Asn Met Glu Thr  
165 170 175

75

Pro Asp Thr His Leu Ser Tyr Lys Pro Gly Lys Gly Asp Glu Asn Ser  
 180 185 190

Lys Ala Met Leu Gly Gln Gln Ser Met  
 195 200

## (2) INFORMATION FOR SEQ ID NO:7:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 567 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: DNA (genomic)

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

CCT TGC GAA TGG GAT GAA GCT GCT ACT GCT CTT GAA ATA AAC CTA GAA	48
Pro Cys Glu Trp Asp Glu Ala Ala Thr Ala Leu Glu Ile Asn Leu Glu	
1 5 10 15	
GAA GAG GAC GAT GAC AAC GAA GAC GAA GTA GAC GAG CAA GCT GAG CAG	96
Glu Glu Asp Asp Asp Asn Glu Asp Glu Val Asp Glu Gln Ala Glu Gln	
20 25 30	
CAA AAA ACT CAC GTA TTT GGG CAG GCG CCT TAT TCT GGT ATA AAT ATT	144
Gln Lys Thr His Val Phe Gly Gln Ala Pro Tyr Ser Gly Ile Asn Ile	
35 40 45	
ACA AAG GAG GGT ATT CAA ATA GGT GTC GAA GGT CAA ACA CCT AAA TAT	192
Thr Lys Glu Gly Ile Gln Ile Gly Val Glu Gly Gln Thr Pro Lys Tyr	
50 55 60	
GCC GAT AAA ACA TTT CAA CCT GAA CCT CAA ATA GGA GAA TCT CAG TGG	240
Ala Asp Lys Thr Phe Gln Pro Glu Pro Gln Ile Gly Glu Ser Gln Trp	
65 70 75 80	
TAC GAA ACT GAA ATT AAT CAT GCA GCT GGG AGA GTC CTT AAA AAG ACT	288
Tyr Glu Thr Glu Ile Asn His Ala Ala Gly Arg Val Leu Lys Lys Thr	
85 90 95	
ACC CCA ATG AAA CCA TGT TAC GGT TCA TAT GCA AAA CCC ACA AAT GAA	336
Thr Pro Met Lys Pro Cys Tyr Gly Ser Tyr Ala Lys Pro Thr Asn Glu	
100 105 110	
AAT GGA GGG CAA GGC ATT CTT GTA AAG CAA CAA AAT GGA AAG CTA GAA	384
Asn Gly Gly Gln Gly Ile Leu Val Lys Gln Gln Asn Gly Lys Leu Glu	
115 120 125	
AGT CAA GTG GAA ATG CAA TTT TTC TCA ACT ACT GAG GCG ACC GCA GGC	432
Ser Gln Val Glu Met Gln Phe Phe Ser Thr Thr Glu Ala Thr Ala Gly	
130 135 140	
AAT GGT GAT AAC TTG ACT CCT AAA GTG GTA TTG TAC AGT GAA GAT GTA	480
Asn Gly Asp Asn Leu Thr Pro Lys Val Val Leu Tyr Ser Glu Asp Val	
145 150 155 160	
GAT ATA GAA ACC CCA GAC ACT CAT ATT TCT TAC ATG CCC ACT ATT AAG	528
Asp Ile Glu Thr Pro Asp Thr His Ile Ser Tyr Met Pro Thr Ile Lys	
165 170 175	
GAA GGT AAC TCA CGA GAA CTA ATG GGC CAA CAA TCT ATG	567

76

Glu Gly Asn Ser Arg Glu Leu Met Gly Gln Gln Ser Met  
 180 185

## (2) INFORMATION FOR SEQ ID NO:8:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 189 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Pro Cys Glu Trp Asp Glu Ala Ala Thr Ala Leu Glu Ile Asn Leu Glu  
 1 5 10 15  
 Glu Glu Asp Asp Asp Asn Glu Asp Glu Val Asp Glu Gln Ala Glu Gln  
 20 25 30  
 Gln Lys Thr His Val Phe Gly Gln Ala Pro Tyr Ser Gly Ile Asn Ile  
 35 40 45  
 Thr Lys Glu Gly Ile Gln Ile Gly Val Glu Gly Gln Thr Pro Lys Tyr  
 50 55 60  
 Ala Asp Lys Thr Phe Gln Pro Glu Pro Gln Ile Gly Glu Ser Gln Trp  
 65 70 75 80  
 Tyr Glu Thr Glu Ile Asn His Ala Ala Gly Arg Val Leu Lys Lys Thr  
 85 90 95  
 Thr Pro Met Lys Pro Cys Tyr Gly Ser Tyr Ala Lys Pro Thr Asn Glu  
 100 105 110  
 Asn Gly Gly Gln Gly Ile Leu Val Lys Gln Gln Asn Gly Lys Leu Glu  
 115 120 125  
 Ser Gln Val Glu Met Gln Phe Phe Ser Thr Thr Glu Ala Thr Ala Gly  
 130 135 140  
 Asn Gly Asp Asn Leu Thr Pro Lys Val Val Leu Tyr Ser Glu Asp Val  
 145 150 155 160  
 Asp Ile Glu Thr Pro Asp Thr His Ile Ser Tyr Met Pro Thr Ile Lys  
 165 170 175  
 Glu Gly Asn Ser Arg Glu Leu Met Gly Gln Gln Ser Met  
 180 185

## (2) INFORMATION FOR SEQ ID NO:9:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 153 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: double  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

ACC GAA GAT AGC GGC CGG GCA GTT GCC GAG GAT GAA GAA GAG GAA GAT

77

Thr Glu Asp Ser Gly Arg Ala Val Ala Glu Asp Glu Glu Glu Glu Asp  
 1 5 10 15  
 GAA GAT GAA GAA GAG GAA GAA GAA GAG CAA AAC GCT CGA GAT CAG GCT 96  
 Glu Asp Glu Glu Glu Glu Glu Glu Glu Gln Asn Ala Arg Asp Gln Ala  
 20 25 30  
 ACT AAG AAA ACA CAT GTC TAT GCC CAG GCT CCT TTG TCT GGA GAA ACA 144  
 Thr Lys Lys Thr His Val Tyr Ala Gln Ala Pro Leu Ser Gly Glu Thr  
 35 40 45  
 ATT ACA AAA 153  
 Ile Thr Lys  
 50

## (2) INFORMATION FOR SEQ ID NO:10:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 51 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Thr Glu Asp Ser Gly Arg Ala Val Ala Glu Asp Glu Glu Glu Glu Asp  
 1 5 10 15  
 Glu Asp Glu Glu Glu Glu Glu Glu Glu Gln Asn Ala Arg Asp Gln Ala  
 20 25 30  
 Thr Lys Lys Thr His Val Tyr Ala Gln Ala Pro Leu Ser Gly Glu Thr  
 35 40 45  
 Ile Thr Lys  
 50

## (2) INFORMATION FOR SEQ ID NO:11:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 135 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: double
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

GCT GCT ACT GCT CTT GAA ATA AAC CTA GAA GAA GAG GAC GAT GAC AAC 48  
 Ala Ala Thr Ala Leu Glu Ile Asn Leu Glu Glu Glu Asp Asp Asp Asn  
 1 5 10 15  
 GAA GAC GAA GTA GAC GAG CAA GCT GAG CAG CAA AAA ACT CAC GTA TTT 96  
 Glu Asp Glu Val Asp Glu Gln Ala Glu Gln Gln Lys Thr His Val Phe  
 20 25 30  
 GGG CAG GCG CCT TAT TCT GGT ATA AAT ATT ACA AAG GAG 135  
 Gly Gln Ala Pro Tyr Ser Gly Ile Asn Ile Thr Lys Glu  
 35 40 45

78

## (2) INFORMATION FOR SEQ ID NO:12:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 45 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Ala	Ala	Thr	Ala	Leu	Glu	Ile	Asn	Leu	Glu	Glu	Glu	Asp	Asp	Asp	Asn
1				5					10					15	
Glu	Asp	Glu	Val	Asp	Glu	Gln	Ala	Glu	Gln	Gln	Lys	Thr	His	Val	Phe
			20					25					30		
Gly	Gln	Ala	Pro	Tyr	Ser	Gly	Ile	Asn	Ile	Thr	Lys	Glu			
		35					40					45			

## (2) INFORMATION FOR SEQ ID NO:13:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 33 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

TCA	GAC	AAT	GCA	GAA	ACA	CAA	GCT	AAA	CCT	GTA
Ser	Asp	Asn	Ala	Glu	Thr	Gln	Ala	Lys	Pro	Val
1				5					10	

33

## (2) INFORMATION FOR SEQ ID NO:14:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 11 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Ser	Asp	Asn	Ala	Glu	Thr	Gln	Ala	Lys	Pro	Val
1				5					10	

## (2) INFORMATION FOR SEQ ID NO:15:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 21 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: double
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

79

GTC GAA GGT CAA ACA CCT AAA  
Val Glu Gly Gln Thr Pro Lys  
1 5

21

## (2) INFORMATION FOR SEQ ID NO:16:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 7 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Val Glu Gly Gln Thr Pro Lys  
1 5

## (2) INFORMATION FOR SEQ ID NO:17:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 24 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: double
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

AAC GAA GCT GAT GCT AAT GCG GCA  
Asn Glu Ala Asp Ala Asn Ala Ala  
1 5

24

## (2) INFORMATION FOR SEQ ID NO:18:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 8 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

Asn Glu Ala Asp Ala Asn Ala Ala  
1 5

## (2) INFORMATION FOR SEQ ID NO:19:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 24 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: double
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

TAC GAA ACT GAA ATT AAT CAT GCA  
Tyr Glu Thr Glu Ile Asn His Ala  
1 5

24

80

## (2) INFORMATION FOR SEQ ID NO:20:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 8 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

Tyr Glu Thr Glu Ile Asn His Ala  
 1 5

## (2) INFORMATION FOR SEQ ID NO:21:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 42 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: double
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

TCC GTT CTG GTT CCG GAT GAA AAA GGG GTG CCT CTT CCA AAG  
 Ser Val Leu Val Pro Asp Glu Lys Gly Val Pro Leu Pro Lys  
 1 5 10

42

## (2) INFORMATION FOR SEQ ID NO:22:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 14 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

Ser Val Leu Val Pro Asp Glu Lys Gly Val Pro Leu Pro Lys  
 1 5 10

## (2) INFORMATION FOR SEQ ID NO:23:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 42 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

GGC ATT CTT GTA AAG CAA CAA AAT GGA AAG CTA GAA AGT CAA  
 Gly Ile Leu Val Lys Gln Gln Asn Gly Lys Leu Glu Ser Gln  
 1 5 10

42

## (2) INFORMATION FOR SEQ ID NO:24:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 14 amino acids

81

- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

Gly Ile Leu Val Lys Gln Gln Asn Gly Lys Leu Glu Ser Gln  
 1 5 10

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 51 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

TCA AAT ACT ACC TCT TTG AAC GAC CGG CAA GGC AAT GCT ACT AAA CCA 48  
 Ser Asn Thr Thr Ser Leu Asn Asp Arg Gln Gly Asn Ala Thr Lys Pro  
 1 5 10 15

AAA 51  
 Lys

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

Ser Asn Thr Thr Ser Leu Asn Asp Arg Gln Gly Asn Ala Thr Lys Pro  
 1 5 10 15

Lys

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 48 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

TCA ACT ACT GAG GCG ACC GCA GGC AAT GGT GAT AAC TTG ACT CCT AAA 48  
 Ser Thr Thr Glu Ala Thr Ala Gly Asn Gly Asp Asn Leu Thr Pro Lys  
 1 5 10 15

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:

82

- (A) LENGTH: 16 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

Ser Thr Thr Glu Ala Thr Ala Gly Asn Gly Asp Asn Leu Thr Pro Lys  
 1 5 10 15

(2) INFORMATION FOR SEQ ID NO:29:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 24 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: double
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

TTG TAC AGT GAA GAT GTA AAT ATG  
 Leu Tyr Ser Glu Asp Val Asn Met  
 1 5

24

(2) INFORMATION FOR SEQ ID NO:30:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 8 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

Leu Tyr Ser Glu Asp Val Asn Met  
 1 5

(2) INFORMATION FOR SEQ ID NO:31:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 24 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: double
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

TTG TAC AGT GAA GAT GTA GAT ATA  
 Leu Tyr Ser Glu Asp Val Asp Ile  
 1 5

24

(2) INFORMATION FOR SEQ ID NO:32:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 8 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

Leu Tyr Ser Glu Asp Val Asp Ile  
1 5

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 36 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

GGA AAA GGT GAT GAA AAT TCT AAA GCT ATG TTG GGT  
Gly Lys Gly Asp Glu Asn Ser Lys Ala Met Leu Gly  
1 5 10

36

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 12 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

Gly Lys Gly Asp Glu Asn Ser Lys Ala Met Leu Gly  
1 5 10

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 36 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

ACT ATT AAG GAA GGT AAC TCA CGA GAA CTA ATG GGC  
Thr Ile Lys Glu Gly Asn Ser Arg Glu Leu Met Gly  
1 5 10

36

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 12 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

84

Thr Ile Lys Glu Gly Asn Ser Arg Glu Leu Met Gly  
 1 5 10

## (2) INFORMATION FOR SEQ ID NO:37:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 165 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: DNA (genomic)

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

AAT TAT TGT TTT CCT CTT GGG GGT ATT GGG GTA ACT GAC ACC TAT CAA	48
Asn Tyr Cys Phe Pro Leu Gly Gly Ile Gly Val Thr Asp Thr Tyr Gln	
1 5 10 15	
GCT ATT AAG GCT AAT GGC AAT GGC TCA GGC GAT AAT GGA GAT ACT ACA	96
Ala Ile Lys Ala Asn Gly Asn Gly Ser Gly Asp Asn Gly Asp Thr Thr	
20 25 30	
TGG ACA AAA GAT GAA ACT TTT GCA ACA CGT AAT GAA ATA GGA GTG GGT	144
Trp Thr Lys Asp Glu Thr Phe Ala Thr Arg Asn Glu Ile Gly Val Gly	
35 40 45	
AAC AAC TTT GCC ATG GAA ATT	165
Asn Asn Phe Ala Met Glu Ile	
50 55	

## (2) INFORMATION FOR SEQ ID NO:38:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 55 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

Asn Tyr Cys Phe Pro Leu Gly Gly Ile Gly Val Thr Asp Thr Tyr Gln	15
1 5 10	
Ala Ile Lys Ala Asn Gly Asn Gly Ser Gly Asp Asn Gly Asp Thr Thr	30
20 25	
Trp Thr Lys Asp Glu Thr Phe Ala Thr Arg Asn Glu Ile Gly Val Gly	45
35 40	
Asn Asn Phe Ala Met Glu Ile	55
50	

## (2) INFORMATION FOR SEQ ID NO:39:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 153 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: DNA (genomic)

85

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

AAT TAC TGC TTT CCA CTG GGA GGT GTG ATT AAT ACA GAG ACT CTT ACC	48
Asn Tyr Cys Phe Pro Leu Gly Gly Val Ile Asn Thr Glu Thr Leu Thr	
1 5 10 15	
AAG GTA AAA CCT AAA ACA GGT CAG GAA AAT GGA TGG GAA AAA GAT GCT	96
Lys Val Lys Pro Lys Thr Gly Gln Glu Asn Gly Trp Glu Lys Asp Ala	
20 25 30	
ACA GAA TTT TCA GAT AAA AAT GAA ATA AGA GTT GGA AAT AAT TTT GCC	144
Thr Glu Phe Ser Asp Lys Asn Glu Ile Arg Val Gly Asn Asn Phe Ala	
35 40 45	
ATG GAA ATC	153
Met Glu Ile	
50	

## (2) INFORMATION FOR SEQ ID NO:40:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 51 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

Asn Tyr Cys Phe Pro Leu Gly Gly Val Ile Asn Thr Glu Thr Leu Thr	
1 5 10 15	
Lys Val Lys Pro Lys Thr Gly Gln Glu Asn Gly Trp Glu Lys Asp Ala	
20 25 30	
Thr Glu Phe Ser Asp Lys Asn Glu Ile Arg Val Gly Asn Asn Phe Ala	
35 40 45	
Met Glu Ile	
50	

## (2) INFORMATION FOR SEQ ID NO:41:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 54 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: DNA (genomic)

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

GTA ACT GAC ACC TAT CAA GCT ATT AAG GCT AAT GGC AAT GGC TCA GGC	48
Val Thr Asp Thr Tyr Gln Ala Ile Lys Ala Asn Gly Asn Gly Ser Gly	
1 5 10 15	
GAT AAT	54
Asp Asn	

## (2) INFORMATION FOR SEQ ID NO:42:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18 amino acids

86

(B) TYPE: amino acid  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

Val Thr Asp Thr Tyr Gln Ala Ile Lys Ala Asn Gly Asn Gly Ser Gly  
1 5 10 15

Asp Asn

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 87 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: double  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

AAT ACA GAG ACT CTT ACC AAG GTA AAA CCT AAA ACA GGT CAG GAA AAT 48  
Asn Thr Glu Thr Leu Thr Lys Val Lys Pro Lys Thr Gly Gln Glu Asn  
1 5 10 15

GGA TGG GAA AAA GAT GCT ACA GAA TTT TCA GAT AAA AAT 87  
Gly Trp Glu Lys Asp Ala Thr Glu Phe Ser Asp Lys Asn  
20 25

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 29 amino acids  
(B) TYPE: amino acid  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

Asn Thr Glu Thr Leu Thr Lys Val Lys Pro Lys Thr Gly Gln Glu Asn  
1 5 10 15

Gly Trp Glu Lys Asp Ala Thr Glu Phe Ser Asp Lys Asn  
20 25

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 21 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: double  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

ACT TTT GCA ACA CGT AAT GAA  
Thr Phe Ala Thr Arg Asn Glu  
1 5

21

## (2) INFORMATION FOR SEQ ID NO:46:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 7 amino acids  
(B) TYPE: amino acid  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

Thr Phe Ala Thr Arg Asn Glu  
1 5

## (2) INFORMATION FOR SEQ ID NO:47:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 24 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: double  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

ACA GAA TTT TCA GAT AAA AAT GAA  
Thr Glu Phe Ser Asp Lys Asn Glu  
1 5

24

## (2) INFORMATION FOR SEQ ID NO:48:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 8 amino acids  
(B) TYPE: amino acid  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

Thr Glu Phe Ser Asp Lys Asn Glu  
1 5

## (2) INFORMATION FOR SEQ ID NO:49:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 24 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: double  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

GAC TAC AAA GAC GAC GAC GAC AAA  
Asp Tyr Lys Asp Asp Asp Asp Lys  
1 5

24

## (2) INFORMATION FOR SEQ ID NO:50:

- (i) SEQUENCE CHARACTERISTICS:

88

- (A) LENGTH: 8 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

Asp Tyr Lys Asp Asp Asp Asp Lys  
 1 5

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2907 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

ATG GCT ACC CCT TCG ATG ATG CCG CAG TGG TCT TAC ATG CAC ATC TCG	48
Ala Thr Pro Ser Met Met Pro Gln Trp Ser Tyr Met His Ile Ser	15
1 5 10	
GGC CAG GAC GCC TCG GAG TAC CTG AGC CCC GGG CTG GTG CAG TTT GCC	96
Gly Gln Asp Ala Ser Glu Tyr Leu Ser Pro Gly Leu Val Gln Phe Ala	30
20 25	
CGC GCC ACC GAG ACG TAC TTC AGC CTG AAT AAC AAG TTT AGA AAC CCC	144
Arg Ala Thr Glu Thr Tyr Phe Ser Leu Asn Asn Lys Phe Arg Asn Pro	45
35 40	
ACG GTG GCA CCT ACG CAC GAC GTA ACC ACA GAC CGG TCC CAG CGT TTG	192
Thr Val Ala Pro Thr His Asp Val Thr Thr Asp Arg Ser Gln Arg Leu	60
50 55 60	
ACG CTG CGG TTC ATC CCT GTG GAC CGC GAG GAT ACC GCG TAC TCG TAC	240
Thr Leu Arg Phe Ile Pro Val Asp Arg Glu Asp Thr Ala Tyr Ser Tyr	75
65 70 75	
AAA GCG CGG TTC ACC CTG GCT GTG GGT GAC AAC CGT GTG CTT GAT ATG	288
Lys Ala Arg Phe Thr Leu Ala Val Gly Asp Asn Arg Val Leu Asp Met	95
80 85 90 95	
GCT TCC ACG TAC TTT GAC ATC CGC GGC GTG CTG GAC AGG GGG CCT ACT	336
Ala Ser Thr Tyr Phe Asp Ile Arg Gly Val Leu Asp Arg Gly Pro Thr	110
100 105 110	
TTT AAG CCC TAC TCC GGC ACT GCC TAC AAC GCT CTA GCT CCC AAG GGC	384
Phe Lys Pro Tyr Ser Gly Thr Ala Tyr Asn Ala Leu Ala Pro Lys Gly	125
115 120 125	
GCT CCT AAC TCC TGT GAG TGG GAA CAA ACC GAA GAT AGC GGC CGG GCA	432
Ala Pro Asn Ser Cys Glu Trp Glu Gln Thr Glu Asp Ser Gly Arg Ala	140
130 135 140	
GTT GCC GAG GAT GAA GAA GAG GAA GAT GAA GAT GAA GAA GAG GAA GAA	480
Val Ala Glu Asp Glu Glu Glu Glu Asp Glu Asp Glu Glu Glu Glu Glu	155
145 150 155	

GAA Glu 160	GAG Glu	CAA Gln	AAC Asn	GCT Ala	CGA Arg 165	GAT Asp	CAG Gln	GCT Ala	ACT Thr	AAG Lys 170	AAA Lys	ACA Thr	CAT His	GTC Val	TAT Tyr 175	528
GCC Ala	CAG Gln	GCT Ala	CCT Pro	TTG Leu 180	TCT Ser	GGA Gly	GAA Glu	ACA Thr	ATT Ile 185	ACA Thr	AAA Lys	AGC Ser	GGG Gly	CTA Leu 190	CAA Gln	576
ATA Ile	GGA Gly	TCA Ser	GAC Asp 195	AAT Asn	GCA Ala	GAA Glu	ACA Thr	CAA Gln	GCT Ala 200	AAA Lys	CCT Pro	GTA Val	TAC Tyr 205	GCA Ala	GAT Asp	624
CCT Pro	TCC Ser	TAT Tyr 210	CAA Gln	CCA Pro	GAA Glu	CCT Pro	CAA Gln	ATT Ile	GGC Gly 215	GAA Glu	TCT Ser	CAG Gln	TGG Trp 220	AAC Asn	GAA Glu	672
GCT Ala 225	GAT Asp	GCT Ala	AAT Asn	GCG Ala	GCA Ala	GGA Gly 230	GGG Gly	AGA Arg	GTG Val	CTT Leu	AAA Lys 235	AAA Lys	ACA Thr	ACT Thr	CCC Pro	720
ATG Met 240	AAA Lys	CCA Pro	TGC Cys	TAT Tyr	GGA Gly 245	TCT Ser	TAT Tyr	GCC Ala	AGG Arg	CCT Pro 250	ACA Thr	AAT Asn	CCT Pro	TTT Phe	GGT Gly 255	768
GGT Gly	CAA Gln	TCC Ser	GTT Val	CTG Leu 260	GTT Val	CCG Pro	GAT Asp	GAA Glu	AAA Lys 265	GGG Gly	GTG Val	CCT Pro	CTT Leu	CCA Pro	AAG Lys 270	816
GTT Val	GAC Asp	TTG Leu	CAA Gln	TTC Phe 275	TTC Phe	TCA Ser	AAT Asn	ACT Thr 280	ACC Thr	TCT Ser	TTG Leu	AAC Asn	GAC Asp 285	CGG Arg	CAA Gln	864
GGC Gly	AAT Asn	GCT Ala 290	ACT Thr	AAA Lys	CCA Pro	AAA Lys	GTG Val 295	GTT Val	TTG Leu	TAC Tyr	AGT Ser	GAA Glu 300	GAT Asp	GTA Val	AAT Asn	912
ATG Met 305	GAA Glu	ACC Thr	CCA Pro	GAC Asp	ACA Thr	CAT His 310	CTG Leu	TCT Ser	TAC Tyr	AAA Lys	CCT Pro 315	GGA Gly	AAA Lys	GGT Gly	GAT Asp	960
GAA Glu 320	AAT Asn	TCT Ser	AAA Lys	GCT Ala	ATG Met 325	TTG Leu	GGT Gly	CAA Gln	CAA Gln	TCT Ser 330	ATG Met	CCA Pro	AAC Asn	AGA Arg	CCC Pro 335	1008
AAT Asn	TAC Tyr	ATT Ile	GCT Ala	TTC Phe 340	AGG Arg	GAC Asp	AAT Asn	TTT Phe 345	ATT Ile	GGC Gly	CTA Leu	ATG Met	TAT Tyr	TAT Tyr	AAC Asn 350	1056
AGC Ser	ACT Thr	GGC Gly	AAC Asn 355	ATG Met	GGT Gly	GTT Val	CTT Leu	GCT Ala 360	GGT Gly	CAG Gln	GCA Ala	TCG Ser	CAG Gln	CTA Leu	AAT Asn	1104
GCC Ala	GTG Val	GTA Val	GAT Asp	TTG Leu 370	CAA Gln	GAC Asp	AGA Arg	AAC Asn	ACA Thr	GAG Glu	CTG Leu	TCC Ser	TAT Tyr	CAA Gln	CTC Leu	1152
TTG Leu 385	CTT Leu	GAT Asp	TCC Ser	ATA Ile	GGT Gly	GAT Asp 390	AGA Arg	ACC Thr	AGA Arg	TAT Tyr	TTT Phe 395	TCT Ser	ATG Met	TGG Trp	AAT Asn	1200
CAG Gln 400	GCT Ala	GTA Val	GAC Asp	AGC Ser	TAT Tyr 405	GAT Asp	CCA Pro	GAT Asp	GTT Val	AGA Arg 410	ATC Ile	ATT Ile	GAA Glu	AAC Asn	CAT His 415	1248

GGA ACT GAG GAT GAA TTG CCA AAT TAT TGT TTT CCT CTT GGG GGT ATT Gly Thr Glu Asp Glu Leu Pro Asn Tyr Cys Phe Pro Leu Gly Gly Ile 420 425 430	1296
GGG GTA ACT GAC ACC TAT CAA GCT ATT AAG GCT AAT GGC AAT GGC TCA Gly Val Thr Asp Thr Tyr Gln Ala Ile Lys Ala Asn Gly Asn Gly Ser 435 440 445	1344
GGC GAT AAT GGA GAT ACT ACA TGG ACA AAA GAT GAA ACT TTT GCA ACA Gly Asp Asn Gly Asp Thr Thr Trp Thr Lys Asp Glu Thr Phe Ala Thr 450 455 460	1392
CGT AAT GAA ATA GGA GTG GGT AAC AAC TTT GCC ATG GAA ATT AAC CTA Arg Asn Glu Ile Gly Val Gly Asn Asn Phe Ala Met Glu Ile Asn Leu 465 470 475	1440
AAT GCC AAC CTA TGG AGA AAT TTC CTT TAC TCC AAT ATT GCG CTG TAC Asn Ala Asn Leu Trp Arg Asn Phe Leu Tyr Ser Asn Ile Ala Leu Tyr 480 485 490 495	1488
CTG CCA GAC AAG CTA AAA TAC AAC CCC ACC AAT GTG GAA ATA TCT GAC Leu Pro Asp Lys Leu Lys Tyr Asn Pro Thr Asn Val Glu Ile Ser Asp 500 505 510	1536
AAC CCC AAC ACC TAC GAC TAC ATG AAC AAG CGA GTG GTG GCT CCC GGG Asn Pro Asn Thr Tyr Asp Tyr Met Asn Lys Arg Val Val Ala Pro Gly 515 520 525	1584
CTT GTA GAC TGC TAC ATT AAC CTT GGG GCG CGC TGG TCT CTG GAC TAC Leu Val Asp Cys Tyr Ile Asn Leu Gly Ala Arg Trp Ser Leu Asp Tyr 530 535 540	1632
ATG GAC AAC GTT AAT CCC TTT AAC CAC CAC CGC AAT GCG GGC CTC CGT Met Asp Asn Val Asn Pro Phe Asn His His Arg Asn Ala Gly Leu Arg 545 550 555	1680
TAT CGC TCC ATG TTG TTG GGA AAC GGC CGC TAC GTG CCC TTT CAC ATT Tyr Arg Ser Met Leu Leu Gly Asn Gly Arg Tyr Val Pro Phe His Ile 560 565 570 575	1728
CAG GTG CCC CAA AAG TTT TTT GCC ATT AAA AAC CTC CTC CTC CTG CCA Gln Val Pro Gln Lys Phe Phe Ala Ile Lys Asn Leu Leu Leu Leu Pro 580 585 590	1776
GGC TCA TAT ACA TAT GAA TGG AAC TTC AGG AAG GAT GTT AAC ATG GTT Gly Ser Tyr Thr Tyr Glu Trp Asn Phe Arg Lys Asp Val Asn Met Val 595 600 605	1824
CTG CAG AGC TCT CTG GGA AAC GAT CTT AGA GTT GAC GGG GCT AGC ATT Leu Gln Ser Ser Leu Gly Asn Asp Leu Arg Val Asp Gly Ala Ser Ile 610 615 620	1872
AAG TTT GAC AGC ATT TGT CTT TAC GCC ACC TTC TTC CCC ATG GCC CAC Lys Phe Asp Ser Ile Cys Leu Tyr Ala Thr Phe Phe Pro Met Ala His 625 630 635	1920
AAC ACG GCC TCC ACG CTG GAA GCC ATG CTC AGA AAT GAC ACC AAC GAC Asn Thr Ala Ser Thr Leu Glu Ala Met Leu Arg Asn Asp Thr Asn Asp 640 645 650 655	1968
CAG TCC TTT AAT GAC TAC CTT TCC GCC GCC AAC ATG CTA TAC CCC ATA Gln Ser Phe Asn Asp Tyr Leu Ser Ala Ala Asn Met Leu Tyr Pro Ile 660 665 670	2016

CCC	GCC	AAC	GCC	ACC	AAC	GTG	CCC	ATC	TCC	ATC	CCA	TCG	CGC	AAC	TGG	2064
Pro	Ala	Asn	Ala	Thr	Asn	Val	Pro	Ile	Ser	Ile	Pro	Ser	Arg	Asn	Trp	
			675					680					685			
GCA	GCA	TTT	CGC	GGT	TGG	GCC	TTC	ACA	CGC	TTG	AAG	ACA	AAG	GAA	ACC	2112
Ala	Ala	Phe	Arg	Gly	Trp	Ala	Phe	Thr	Arg	Leu	Lys	Thr	Lys	Glu	Thr	
		690					695					700				
CCT	TCC	CTG	GGA	TCA	GGC	TAC	GAC	CCT	TAC	TAC	ACC	TAC	TCT	GGC	TCC	2160
Pro	Ser	Leu	Gly	Ser	Gly	Tyr	Asp	Pro	Tyr	Tyr	Thr	Tyr	Ser	Gly	Ser	
	705					710					715					
ATA	CCA	TAC	CTT	GAC	GGA	ACC	TTC	TAT	CTT	AAT	CAC	ACC	TTT	AAG	AAG	2208
Ile	Pro	Tyr	Leu	Asp	Gly	Thr	Phe	Tyr	Leu	Asn	His	Thr	Phe	Lys	Lys	
					725					730					735	
GTG	GCC	ATT	ACC	TTT	GAC	TCT	TCT	GTT	AGC	TGG	CCG	GGC	AAC	GAC	CGC	2256
Val	Ala	Ile	Thr	Phe	Asp	Ser	Ser	Val	Ser	Trp	Pro	Gly	Asn	Asp	Arg	
				740					745					750		
CTG	CTT	ACT	CCC	AAT	GAG	TTT	GAG	ATT	AAA	CGC	TCA	GTT	GAC	GGG	GAG	2304
Leu	Leu	Thr	Pro	Asn	Glu	Phe	Glu	Ile	Lys	Arg	Ser	Val	Asp	Gly	Glu	
			755					760					765			
GGC	TAC	AAC	GTA	GCT	CAG	TGC	AAC	ATG	ACC	AAG	GAC	TGG	TTC	CTG	GTG	2352
Gly	Tyr	Asn	Val	Ala	Gln	Cys	Asn	Met	Thr	Lys	Asp	Trp	Phe	Leu	Val	
		770					775					780				
CAG	ATG	TTG	GCC	AAC	TAC	AAT	ATT	GGC	TAC	CAG	GGC	TTC	TAC	ATT	CCA	2400
Gln	Met	Leu	Ala	Asn	Tyr	Asn	Ile	Gly	Tyr	Gln	Gly	Phe	Tyr	Ile	Pro	
	785					790					795					
GAA	AGC	TAC	AAG	GAC	CGC	ATG	TAC	TCG	TTC	TTC	AGA	AAC	TTC	CAG	CCC	2448
Glu	Ser	Tyr	Lys	Asp	Arg	Met	Tyr	Ser	Phe	Phe	Arg	Asn	Phe	Gln	Pro	
	800				805					810					815	
ATG	AGC	CGG	CAA	GTG	GTT	GAC	GAT	ACT	AAA	TAC	AAG	GAG	TAT	CAG	CAG	2496
Met	Ser	Arg	Gln	Val	Val	Asp	Asp	Thr	Lys	Tyr	Lys	Glu	Tyr	Gln	Gln	
				820					825					830		
GTT	GGA	ATT	CTT	CAC	CAG	CAT	AAC	AAC	TCA	GGA	TTC	GTA	GGC	TAC	CTC	2544
Val	Gly	Ile	Leu	His	Gln	His	Asn	Asn	Ser	Gly	Phe	Val	Gly	Tyr	Leu	
			835					840					845			
GCT	CCC	ACC	ATG	CGC	GAG	GGA	CAG	GCT	TAC	CCC	GCC	AAC	GTG	CCC	TAC	2592
Ala	Pro	Thr	Met	Arg	Glu	Gly	Gln	Ala	Tyr	Pro	Ala	Asn	Val	Pro	Tyr	
		850					855					860				
CCA	CTA	ATA	GGC	AAA	ACC	GCG	GTT	GAC	AGT	ATT	ACC	CAG	AAA	AAG	TTT	2640
Pro	Leu	Ile	Gly	Lys	Thr	Ala	Val	Asp	Ser	Ile	Thr	Gln	Lys	Lys	Phe	
		865				870					875					
CTT	TGC	GAT	CGC	ACC	CTT	TGG	CGC	ATC	CCA	TTC	TCC	AGT	AAC	TTT	ATG	2688
Leu	Cys	Asp	Arg	Thr	Leu	Trp	Arg	Ile	Pro	Phe	Ser	Ser	Asn	Phe	Met	
	880				885					890					895	
TCC	ATG	GGC	GCA	CTC	ACA	GAC	CTG	GGC	CAA	AAC	CTT	CTC	TAC	GCC	AAC	2736
Ser	Met	Gly	Ala	Leu	Thr	Asp	Leu	Gly	Gln	Asn	Leu	Leu	Tyr	Ala	Asn	
				900					905					910		
TCC	GCC	CAC	GCG	CTA	GAC	ATG	ACT	TTT	GAG	GTG	GAT	CCC	ATG	GAC	GAG	2784
Ser	Ala	His	Ala	Leu	Asp	Met	Thr	Phe	Glu	Val	Asp	Pro	Met	Asp	Glu	
			915					920					925			

92

CCC ACC CTT CTT TAT GTT TTG TTT GAA GTC TTT GAC GTG GTC CGT GTG	2832
Pro Thr Leu Leu Tyr Val Leu Phe Glu Val Phe Asp Val Val Arg Val	
930 935 940	
CAC CAG CCG CAC CGC GGC GTC ATC GAG ACC GTG TAC CTG CGC ACG CCC	2880
His Gln Pro His Arg Gly Val Ile Glu Thr Val Tyr Leu Arg Thr Pro	
945 950 955	
TTC TCG GCC GGC AAC GCC ACA ACA TAA	2907
Phe Ser Ala Gly Asn Ala Thr Thr	
960 965	

## (2) INFORMATION FOR SEQ ID NO:52:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 967 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

Ala Thr Pro Ser Met Met Pro Gln Trp Ser Tyr Met His Ile Ser Gly	15
1 5 10	
Gln Asp Ala Ser Glu Tyr Leu Ser Pro Gly Leu Val Gln Phe Ala Arg	30
20 25	
Ala Thr Glu Thr Tyr Phe Ser Leu Asn Asn Lys Phe Arg Asn Pro Thr	45
35 40	
Val Ala Pro Thr His Asp Val Thr Thr Asp Arg Ser Gln Arg Leu Thr	60
50 55	
Leu Arg Phe Ile Pro Val Asp Arg Glu Asp Thr Ala Tyr Ser Tyr Lys	80
65 70 75	
Ala Arg Phe Thr Leu Ala Val Gly Asp Asn Arg Val Leu Asp Met Ala	95
85 90	
Ser Thr Tyr Phe Asp Ile Arg Gly Val Leu Asp Arg Gly Pro Thr Phe	110
100 105	
Lys Pro Tyr Ser Gly Thr Ala Tyr Asn Ala Leu Ala Pro Lys Gly Ala	125
115 120	
Pro Asn Ser Cys Glu Trp Glu Gln Thr Glu Asp Ser Gly Arg Ala Val	140
130 135	
Ala Glu Asp Glu Glu Glu Glu Asp Glu Asp Glu Glu Glu Glu Glu	160
145 150 155	
Glu Gln Asn Ala Arg Asp Gln Ala Thr Lys Lys Thr His Val Tyr Ala	175
165 170	
Gln Ala Pro Leu Ser Gly Glu Thr Ile Thr Lys Ser Gly Leu Gln Ile	190
180 185	
Gly Ser Asp Asn Ala Glu Thr Gln Ala Lys Pro Val Tyr Ala Asp Pro	205
195 200	
Ser Tyr Gln Pro Glu Pro Gln Ile Gly Glu Ser Gln Trp Asn Glu Ala	220
210 215	

Asp Ala Asn Ala Ala Gly Gly Arg Val Leu Lys Lys Thr Thr Pro Met  
 225 230 235 240  
 Lys Pro Cys Tyr Gly Ser Tyr Ala Arg Pro Thr Asn Pro Phe Gly Gly  
 245 250 255  
 Gln Ser Val Leu Val Pro Asp Glu Lys Gly Val Pro Leu Pro Lys Val  
 260 265 270  
 Asp Leu Gln Phe Phe Ser Asn Thr Thr Ser Leu Asn Asp Arg Gln Gly  
 275 280 285  
 Asn Ala Thr Lys Pro Lys Val Val Leu Tyr Ser Glu Asp Val Asn Met  
 290 295 300  
 Glu Thr Pro Asp Thr His Leu Ser Tyr Lys Pro Gly Lys Gly Asp Glu  
 305 310 315 320  
 Asn Ser Lys Ala Met Leu Gly Gln Gln Ser Met Pro Asn Arg Pro Asn  
 325 330 335  
 Tyr Ile Ala Phe Arg Asp Asn Phe Ile Gly Leu Met Tyr Tyr Asn Ser  
 340 345 350  
 Thr Gly Asn Met Gly Val Leu Ala Gly Gln Ala Ser Gln Leu Asn Ala  
 355 360 365  
 Val Val Asp Leu Gln Asp Arg Asn Thr Glu Leu Ser Tyr Gln Leu Leu  
 370 375 380  
 Leu Asp Ser Ile Gly Asp Arg Thr Arg Tyr Phe Ser Met Trp Asn Gln  
 385 390 395 400  
 Ala Val Asp Ser Tyr Asp Pro Asp Val Arg Ile Ile Glu Asn His Gly  
 405 410 415  
 Thr Glu Asp Glu Leu Pro Asn Tyr Cys Phe Pro Leu Gly Gly Ile Gly  
 420 425 430  
 Val Thr Asp Thr Tyr Gln Ala Ile Lys Ala Asn Gly Asn Gly Ser Gly  
 435 440 445  
 Asp Asn Gly Asp Thr Thr Trp Thr Lys Asp Glu Thr Phe Ala Thr Arg  
 450 455 460  
 Asn Glu Ile Gly Val Gly Asn Asn Phe Ala Met Glu Ile Asn Leu Asn  
 465 470 475 480  
 Ala Asn Leu Trp Arg Asn Phe Leu Tyr Ser Asn Ile Ala Leu Tyr Leu  
 485 490 495  
 Pro Asp Lys Leu Lys Tyr Asn Pro Thr Asn Val Glu Ile Ser Asp Asn  
 500 505 510  
 Pro Asn Thr Tyr Asp Tyr Met Asn Lys Arg Val Val Ala Pro Gly Leu  
 515 520 525  
 Val Asp Cys Tyr Ile Asn Leu Gly Ala Arg Trp Ser Leu Asp Tyr Met  
 530 535 540  
 Asp Asn Val Asn Pro Phe Asn His His Arg Asn Ala Gly Leu Arg Tyr  
 545 550 555 560

94

Arg Ser Met Leu Leu Gly Asn Gly Arg Tyr Val Pro Phe His Ile Gln  
 565 570 575  
 Val Pro Gln Lys Phe Phe Ala Ile Lys Asn Leu Leu Leu Leu Pro Gly  
 580 585 590  
 Ser Tyr Thr Tyr Glu Trp Asn Phe Arg Lys Asp Val Asn Met Val Leu  
 595 600 605  
 Gln Ser Ser Leu Gly Asn Asp Leu Arg Val Asp Gly Ala Ser Ile Lys  
 610 615 620  
 Phe Asp Ser Ile Cys Leu Tyr Ala Thr Phe Phe Pro Met Ala His Asn  
 625 630 635 640  
 Thr Ala Ser Thr Leu Glu Ala Met Leu Arg Asn Asp Thr Asn Asp Gln  
 645 650 655  
 Ser Phe Asn Asp Tyr Leu Ser Ala Ala Asn Met Leu Tyr Pro Ile Pro  
 660 665 670  
 Ala Asn Ala Thr Asn Val Pro Ile Ser Ile Pro Ser Arg Asn Trp Ala  
 675 680 685  
 Ala Phe Arg Gly Trp Ala Phe Thr Arg Leu Lys Thr Lys Glu Thr Pro  
 690 695 700  
 Ser Leu Gly Ser Gly Tyr Asp Pro Tyr Tyr Thr Tyr Ser Gly Ser Ile  
 705 710 715 720  
 Pro Tyr Leu Asp Gly Thr Phe Tyr Leu Asn His Thr Phe Lys Lys Val  
 725 730 735  
 Ala Ile Thr Phe Asp Ser Ser Val Ser Trp Pro Gly Asn Asp Arg Leu  
 740 745 750  
 Leu Thr Pro Asn Glu Phe Glu Ile Lys Arg Ser Val Asp Gly Glu Gly  
 755 760 765  
 Tyr Asn Val Ala Gln Cys Asn Met Thr Lys Asp Trp Phe Leu Val Gln  
 770 775 780  
 Met Leu Ala Asn Tyr Asn Ile Gly Tyr Gln Gly Phe Tyr Ile Pro Glu  
 785 790 795 800  
 Ser Tyr Lys Asp Arg Met Tyr Ser Phe Phe Arg Asn Phe Gln Pro Met  
 805 810 815  
 Ser Arg Gln Val Val Asp Asp Thr Lys Tyr Lys Glu Tyr Gln Gln Val  
 820 825 830  
 Gly Ile Leu His Gln His Asn Asn Ser Gly Phe Val Gly Tyr Leu Ala  
 835 840 845  
 Pro Thr Met Arg Glu Gly Gln Ala Tyr Pro Ala Asn Val Pro Tyr Pro  
 850 855 860  
 Leu Ile Gly Lys Thr Ala Val Asp Ser Ile Thr Gln Lys Lys Phe Leu  
 865 870 875 880  
 Cys Asp Arg Thr Leu Trp Arg Ile Pro Phe Ser Ser Asn Phe Met Ser  
 885 890 895

95

Met Gly Ala Leu Thr Asp Leu Gly Gln Asn Leu Leu Tyr Ala Asn Ser  
                   900                                  905                                  910

Ala His Ala Leu Asp Met Thr Phe Glu Val Asp Pro Met Asp Glu Pro  
                   915                                  920                                  925

Thr Leu Leu Tyr Val Leu Phe Glu Val Phe Asp Val Val Arg Val His  
           930                                  935                                  940

Gln Pro His Arg Gly Val Ile Glu Thr Val Tyr Leu Arg Thr Pro Phe  
   945                                  950                                  955                                  960

Ser Ala Gly Asn Ala Thr Thr  
                                   965

## (2) INFORMATION FOR SEQ ID NO:53:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2858 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: double  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: DNA (genomic)

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

ATG GCT ACC CCT TCG ATG ATG CCG CAG TGG TCT TAC ATG CAC ATC TCG Ala Thr Pro Ser Met Met Pro Gln Trp Ser Tyr Met His Ile Ser 1                                  5                                  10                                  15	48
GGC CAG GAC GCC TCG GAG TAC CTG AGC CCC GGG CTG GTG CAG TTT GCC Gly Gln Asp Ala Ser Glu Tyr Leu Ser Pro Gly Leu Val Gln Phe Ala 20                                  25                                  30	96
CGC GCC ACC GAG ACG TAC TTC AGC CTG AAT AAC AAG TTT AGA AAC CCC Arg Ala Thr Glu Thr Tyr Phe Ser Leu Asn Asn Lys Phe Arg Asn Pro 35                                  40                                  45	144
ACG GTG GCG CCT ACG CAC GAC GTG ACC ACA GAC CGG TCC CAG CGT TTG Thr Val Ala Pro Thr His Asp Val Thr Thr Asp Arg Ser Gln Arg Leu 50                                  55                                  60	192
ACG CTG CGG TTC ATC CCT GTG GAC CGT GAG GAT ACT GCG TAC TCG TAC Thr Leu Arg Phe Ile Pro Val Asp Arg Glu Asp Thr Ala Tyr Ser Tyr 65                                  70                                  75	240
AAG GCG CGG TTC ACC CTA GCT GTG GGT GAT AAC CGT GTG CTG GAC ATG Lys Ala Arg Phe Thr Leu Ala Val Gly Asp Asn Arg Val Leu Asp Met 80                                  85                                  90                                  95	288
GCT TCC ACG TAC TTT GAC ATC CGC GGC GTG CTG GAC AGG GGC CCT ACT Ala Ser Thr Tyr Phe Asp Ile Arg Gly Val Leu Asp Arg Gly Pro Thr 100                                  105                                  110	336
TTT AAG CCC TAC TCT GGC ACT GCC TAC AAC GCC CTG GCT CCC AAG GGT Phe Lys Pro Tyr Ser Gly Thr Ala Tyr Asn Ala Leu Ala Pro Lys Gly 115                                  120                                  125	384
GCC CCA AAT CCT TGC GAA TGG GAT GAA GCT GCT ACT GCT CTT GAA ATA Ala Pro Asn Pro Cys Glu Trp Asp Glu Ala Ala Thr Ala Leu Glu Ile 130                                  135                                  140	432
AAC CTA GAA GAA GAG GAC GAT GAC AAC GAA GAC GAA GTA GAC GAG CAA	480

Asn	Leu	Glu	Glu	Glu	Asp	Asp	Asp	Asn	Glu	Asp	Glu	Val	Asp	Glu	Gln		
145						150					155						
GCT	GAG	CAG	CAA	AAA	ACT	CAC	GTA	TTT	GGG	CAG	GCG	CCT	TAT	TCT	GGT	528	
Ala	Glu	Gln	Gln	Lys	Thr	His	Val	Phe	Gly	Gln	Ala	Pro	Tyr	Ser	Gly		
160					165					170					175		
ATA	AAT	ATT	ACA	AAG	GAG	GGT	ATT	CAA	ATA	GGT	GTC	GAA	GGT	CAA	ACA	576	
Ile	Asn	Ile	Thr	Lys	Glu	Gly	Ile	Gln	Ile	Gly	Val	Glu	Gly	Gln	Thr		
				180					185					190			
CCT	AAA	TAT	GCC	GAT	AAA	ACA	TTT	CAA	CCT	GAA	CCT	CAA	ATA	GGA	GAA	624	
Pro	Lys	Tyr	Ala	Asp	Lys	Thr	Phe	Gln	Pro	Glu	Pro	Gln	Ile	Gly	Glu		
			195					200					205				
TCT	CAG	TGG	TAC	GAA	ACT	GAA	ATT	AAT	CAT	GCA	GCT	GGG	AGA	GTC	CTT	672	
Ser	Gln	Trp	Tyr	Glu	Thr	Glu	Ile	Asn	His	Ala	Ala	Gly	Arg	Val	Leu		
		210					215					220					
AAA	AAG	ACT	ACC	CCA	ATG	AAA	CCA	TGT	TAC	GGT	TCA	TAT	GCA	AAA	CCC	720	
Lys	Lys	Thr	Thr	Pro	Met	Lys	Pro	Cys	Tyr	Gly	Ser	Tyr	Ala	Lys	Pro		
		225				230				235							
ACA	AAT	GAA	AAT	GGA	GGG	CAA	GGC	ATT	CTT	GTA	AAG	CAA	CAA	AAT	GGA	768	
Thr	Asn	Glu	Asn	Gly	Gly	Gln	Gly	Ile	Leu	Val	Lys	Gln	Gln	Asn	Gly		
240					245					250					255		
AAG	CTA	GAA	AGT	CAA	GTG	GAA	ATG	CAA	TTT	TTC	TCA	ACT	ACT	GAG	GCG	816	
Lys	Leu	Glu	Ser	Gln	Val	Glu	Met	Gln	Phe	Phe	Ser	Thr	Thr	Glu	Ala		
				260					265					270			
ACC	GCA	GGC	AAT	GGT	GAT	AAC	TTG	ACT	CCT	AAA	GTG	GTA	TTG	TAC	AGT	864	
Thr	Ala	Gly	Asn	Gly	Asp	Asn	Leu	Thr	Pro	Lys	Val	Val	Leu	Tyr	Ser		
			275					280					285				
GAA	GAT	GTA	GAT	ATA	GAA	ACC	CCA	GAC	ACT	CAT	ATT	TCT	TAC	ATG	CCC	912	
Glu	Asp	Val	Asp	Ile	Glu	Thr	Pro	Asp	Thr	His	Ile	Ser	Tyr	Met	Pro		
		290					295					300					
ACT	ATT	AAG	GAA	GGT	AAC	TCA	CGA	GAA	CTA	ATG	GGC	CAA	CAA	TCT	ATG	960	
Thr	Ile	Lys	Glu	Gly	Asn	Ser	Arg	Glu	Leu	Met	Gly	Gln	Gln	Ser	Met		
		305				310					315						
CCC	AAC	AGG	CCT	AAT	TAC	ATT	GCT	TTT	AGG	GAC	AAT	TTT	ATT	GGT	CTA	1008	
Pro	Asn	Arg	Pro	Asn	Tyr	Ile	Ala	Phe	Arg	Asp	Asn	Phe	Ile	Gly	Leu		
320					325					330					335		
ATG	TAT	TAC	AAC	AGC	ACG	GGT	AAT	ATG	GGT	GTT	CTG	GCG	GGC	CAA	GCA	1056	
Met	Tyr	Tyr	Asn	Ser	Thr	Gly	Asn	Met	Gly	Val	Leu	Ala	Gly	Gln	Ala		
				340					345					350			
TCG	CAG	TTG	AAT	GCT	GTT	GTA	GAT	TTG	CAA	GAC	AGA	AAC	ACA	GAG	CTT	1104	
Ser	Gln	Leu	Asn	Ala	Val	Val	Asp	Leu	Gln	Asp	Arg	Asn	Thr	Glu	Leu		
			355					360						365			
TCA	TAC	CAG	CTT	TTG	CTT	GAT	TCC	ATT	GGT	GAT	AGA	ACC	AGG	TAC	TTT	1152	
Ser	Tyr	Gln	Leu	Leu	Leu	Asp	Ser	Ile	Gly	Asp	Arg	Thr	Arg	Tyr	Phe		
			370				375					380					
TCT	ATG	TGG	AAT	CAG	GCT	GTT	GAC	AGC	TAT	GAT	CCA	GAT	GTT	AGA	ATT	1200	
Ser	Met	Trp	Asn	Gln	Ala	Val	Asp	Ser	Tyr	Asp	Pro	Asp	Val	Arg	Ile		
		385				390					395						
ATT	GAA	AAT	CAT	GGA	ACT	GAA	GAT	GAA	CTT	CCA	AAT	TAC	TGC	TTT	CCA	1248	

Ile 400	Glu	Asn	His	Gly	Thr 405	Glu	Asp	Glu	Leu	Pro 410	Asn	Tyr	Cys	Phe	Pro 415	
CTG	GGA	GGT	GTG	ATT	AAT	ACA	GAG	ACT	CTT	ACC	AAG	GTA	AAA	CCT	AAA	1296
Leu	Gly	Gly	Val	Ile 420	Asn	Thr	Glu	Thr	Leu 425	Thr	Lys	Val	Lys	Pro 430	Lys	
ACA	GGT	CAG	GAA	AAT	GGA	TGG	GAA	AAA	GAT	GCT	ACA	GAA	TTT	TCA	GAT	1344
Thr	Gly	Gln	Glu 435	Asn	Gly	Trp	Glu	Lys 440	Asp	Ala	Thr	Glu	Phe 445	Ser	Asp	
AAA	AAT	GAA	ATA	AGA	GTT	GGA	AAT	AAT	TTT	GCC	ATG	GAA	ATC	AAT	CTA	1392
Lys	Asn	Glu 450	Ile	Arg	Val	Gly	Asn 455	Asn	Phe	Ala	Met	Glu 460	Ile	Asn	Leu	
AAT	GCC	AAC	CTG	TGG	AGA	AAT	TTC	CTG	TAC	TCC	AAC	ATA	GCG	CTG	TAT	1440
Asn	Ala	Asn	Leu	Trp	Arg	Asn 470	Phe	Leu	Tyr	Ser	Asn 475	Ile	Ala	Leu	Tyr	
TTG	CCC	GAC	AAG	CTA	AAG	TAC	AGT	CCT	TCC	AAC	GTA	AAA	ATT	TCT	GAT	1488
Leu 480	Pro	Asp	Lys	Leu	Lys 485	Tyr	Ser	Pro	Ser	Asn 490	Val	Lys	Ile	Ser	Asp 495	
AAC	CCA	AAC	ACC	TAC	GAC	TAC	ATG	AAC	AAG	CGA	GTG	GTG	GCT	CCC	GGG	1536
Asn	Pro	Asn	Thr 500	Tyr	Asp	Tyr	Met	Asn 505	Lys	Arg	Val	Val	Ala	Pro 510	Gly	
TTA	GTG	GAC	TGC	TAC	ATT	AAC	CTT	GGA	GCA	CGC	TGG	TCC	CTT	GAC	TAT	1584
Leu	Val	Asp	Cys 515	Tyr	Ile	Asn	Leu	Gly 520	Ala	Arg	Trp	Ser	Leu 525	Asp	Tyr	
ATG	GAC	AAC	GTC	AAC	CCA	TTT	AAC	CAC	CAC	CGC	AAT	GCT	GGC	CTG	CGC	1632
Met	Asp	Asn 530	Val	Asn	Pro	Phe	Asn 535	His	His	Arg	Asn 540	Ala	Gly	Leu	Arg	
TAC	CGC	TCA	ATG	TTG	CTG	GGC	AAT	GGT	CGC	TAT	GTG	CCC	TTC	CAC	ATC	1680
Tyr	Arg	Ser	Met	Leu	Leu	Gly 550	Asn	Gly	Arg	Tyr	Val 555	Pro	Phe	His	Ile	
CAG	GTG	CCT	CAG	AAG	TTC	TTT	GCC	ATT	AAA	AAC	CTC	CTT	CTC	CTG	CCG	1728
Gln	Val	Pro	Gln	Lys	Phe 565	Phe	Ala	Ile	Lys	Asn 570	Leu	Leu	Leu	Leu	Pro 575	
GGC	TCA	TAC	ACC	TAC	GAG	TGG	AAC	TTC	AGG	AAG	GAT	GTT	AAC	ATG	GTT	1776
Gly	Ser	Tyr	Thr 580	Tyr	Glu	Trp	Asn	Phe	Arg 585	Lys	Asp	Val	Asn 590	Met	Val	
CTG	CAG	AGC	TCC	CTA	GGA	AAT	GAC	CTA	AGG	GTT	GAC	GGA	GCC	AGC	ATT	1824
Leu	Gln	Ser	Ser 595	Leu	Gly	Asn	Asp	Leu 600	Arg	Val	Asp	Gly 605	Ala	Ser	Ile	
AAG	TTT	GAT	AGC	ATT	TGC	CTT	TAC	GCC	ACC	TTC	TTC	CCC	ATG	GCC	CAC	1872
Lys	Phe	Asp 610	Ser	Ile	Cys	Leu	Tyr 615	Ala	Thr	Phe	Phe 620	Pro	Met	Ala	His	
AAC	ACC	GCC	TCC	ACG	CTT	GAG	GCC	ATG	CTT	AGA	AAC	GAC	ACC	AAC	GAC	1920
Asn	Thr	Ala	Ser	Thr	Leu	Glu 630	Ala	Met	Leu	Arg	Asn 635	Asp	Thr	Asn	Asp	
CAG	TCC	TTT	AAC	GAC	TAT	CTC	TCC	GCC	GCC	AAC	ATG	CTC	TAC	CCT	ATA	1968
Gln	Ser	Phe	Asn	Asp 645	Tyr	Leu	Ser	Ala	Ala 650	Asn	Met	Leu	Tyr	Pro 655	Ile	

CCC GCC AAC GCT ACC AAC GTG CCC ATA TCC ATC CCC TCC CGC AAC TGG Pro Ala Asn Ala Thr Asn Val Pro Ile Ser Ile Pro Ser Arg Asn Trp 660 665 670	2016
GCG GCT TTC CGC GGC TGG GCC TTC ACG CGC CTT AAG ACT AAG GAA ACC Ala Ala Phe Arg Gly Trp Ala Phe Thr Arg Leu Lys Thr Lys Glu Thr 675 680 685	2064
CCA TCA CTG GGC TCG GGC TAC GAC CCT TAT TAC ACC TAC TCT GGC TCT Pro Ser Leu Gly Ser Gly Tyr Asp Pro Tyr Tyr Thr Tyr Ser Gly Ser 690 695 700	2112
ATA CCC TAC CTA GAT GGA ACC TTT TAC CTC AAC CAC ACC TTT AAG AAG Ile Pro Tyr Leu Asp Gly Thr Phe Tyr Leu Asn His Thr Phe Lys Lys 705 710 715	2160
GTG GCC ATT ACC TTT GAC TCT TCT GTC AGC TGG CCT GGC AAT GAC CGC Val Ala Ile Thr Phe Asp Ser Ser Val Ser Trp Pro Gly Asn Asp Arg 720 725 730 735	2208
CTG CTT ACC CCC AAC GAG TTT GAA ATT AAG CGC TCA GTT GAC GGG GAG Leu Leu Thr Pro Asn Glu Phe Glu Ile Lys Arg Ser Val Asp Gly Glu 740 745 750	2256
GGT TAC AAC GTT GCC CAG TGT AAC ATG ACC AAA GAC TGG TTC CTG GTA Gly Tyr Asn Val Ala Gln Cys Asn Met Thr Lys Asp Trp Phe Leu Val 755 760 765	2304
CAA ATG CTA GCT AAC TAC AAC ATT GGC TAC CAG GGC TTC TAT ATC CCA Gln Met Leu Ala Asn Tyr Asn Ile Gly Tyr Gln Gly Phe Tyr Ile Pro 770 775 780	2352
GAG AGC TAC AAG GAC CGC ATG TAC TCC TTC TTT AGA AAC TTC CAG CCC Glu Ser Tyr Lys Asp Arg Met Tyr Ser Phe Phe Arg Asn Phe Gln Pro 785 790 795	2400
ATG AGC CGT CAG GTG GTG GAT GAT ACT AAA TAC AAG GAC TAC CAA CAG Met Ser Arg Gln Val Val Asp Asp Thr Lys Tyr Lys Asp Tyr Gln Gln 800 805 810 815	2448
GTG GGC ATC CTA CAC CAA CAC AAC AAC TCT GGA TTT GTT GGC TAC CTT Val Gly Ile Leu His Gln His Asn Asn Ser Gly Phe Val Gly Tyr Leu 820 825 830	2496
GCC CCC ACC ATG CGC GAA GGA CAG GCC TAC CCT GCT AAC TTC CCC TAT Ala Pro Thr Met Arg Glu Gly Gln Ala Tyr Pro Ala Asn Phe Pro Tyr 835 840 845	2544
CCG CTT ATA GGC AAG ACC GCA GTT GAC AGC ATT ACC CAG AAA AAG TTT Pro Leu Ile Gly Lys Thr Ala Val Asp Ser Ile Thr Gln Lys Lys Phe 850 855 860	2592
CTT TGC GAT CGC ACC CTT TGG CGC ATC CCA TTC TCC AGT AAC TTT ATG Leu Cys Asp Arg Thr Leu Trp Arg Ile Pro Phe Ser Ser Asn Phe Met 865 870 875	2640
TCC ATG GGC GCA CTC ACA GAC CTG GGC CAA AAC CTT CTC TAC GCC AAC Ser Met Gly Ala Leu Thr Asp Leu Gly Gln Asn Leu Leu Tyr Ala Asn 880 885 890 895	2688
TCC GCC CAC GCG CTA GAC ATG ACT TTT GAG GTG GAT CCC ATG GAC GAG Ser Ala His Ala Leu Asp Met Thr Phe Glu Val Asp Pro Met Asp Glu 900 905 910	2736

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CCC ACC CTT CTT TAT GTT TTG TTT GAA GTC TTT GAC GTG GTC CGT GTG	2784
Pro Thr Leu Leu Tyr Val Leu Phe Glu Val Phe Asp Val Val Arg Val	
915 920 925	
CAC CGG CCG CAC CGC GGC GTC ATC GAA ACC GTG TAC CTG CGC ACG CCC	2832
His Arg Pro His Arg Gly Val Ile Glu Thr Val Tyr Leu Arg Thr Pro	
930 935 940	
TTC TCG GCC GGC AAC GCA CAA CAT AA	2858
Phe Ser Ala Gly Asn Ala Gln His	
945 950	

## (2) INFORMATION FOR SEQ ID NO:54:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 951 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

Ala Thr Pro Ser Met Met Pro Gln Trp Ser Tyr Met His Ile Ser Gly	
1 5 10 15	
Gln Asp Ala Ser Glu Tyr Leu Ser Pro Gly Leu Val Gln Phe Ala Arg	
20 25 30	
Ala Thr Glu Thr Tyr Phe Ser Leu Asn Asn Lys Phe Arg Asn Pro Thr	
35 40 45	
Val Ala Pro Thr His Asp Val Thr Thr Asp Arg Ser Gln Arg Leu Thr	
50 55 60	
Leu Arg Phe Ile Pro Val Asp Arg Glu Asp Thr Ala Tyr Ser Tyr Lys	
65 70 75 80	
Ala Arg Phe Thr Leu Ala Val Gly Asp Asn Arg Val Leu Asp Met Ala	
85 90 95	
Ser Thr Tyr Phe Asp Ile Arg Gly Val Leu Asp Arg Gly Pro Thr Phe	
100 105 110	
Lys Pro Tyr Ser Gly Thr Ala Tyr Asn Ala Leu Ala Pro Lys Gly Ala	
115 120 125	
Pro Asn Pro Cys Glu Trp Asp Glu Ala Ala Thr Ala Leu Glu Ile Asn	
130 135 140	
Leu Glu Glu Glu Asp Asp Asp Asn Glu Asp Glu Val Asp Glu Gln Ala	
145 150 155 160	
Glu Gln Gln Lys Thr His Val Phe Gly Gln Ala Pro Tyr Ser Gly Ile	
165 170 175	
Asn Ile Thr Lys Glu Gly Ile Gln Ile Gly Val Glu Gly Gln Thr Pro	
180 185 190	
Lys Tyr Ala Asp Lys Thr Phe Gln Pro Glu Pro Gln Ile Gly Glu Ser	
195 200 205	
Gln Trp Tyr Glu Thr Glu Ile Asn His Ala Ala Gly Arg Val Leu Lys	
210 215 220	

100

Lys Thr Thr Pro Met Lys Pro Cys Tyr Gly Ser Tyr Ala Lys Pro Thr  
 225 230 235 240  
 Asn Glu Asn Gly Gly Gln Gly Ile Leu Val Lys Gln Gln Asn Gly Lys  
 245 250 255  
 Leu Glu Ser Gln Val Glu Met Gln Phe Phe Ser Thr Thr Glu Ala Thr  
 260 265 270  
 Ala Gly Asn Gly Asp Asn Leu Thr Pro Lys Val Val Leu Tyr Ser Glu  
 275 280 285  
 Asp Val Asp Ile Glu Thr Pro Asp Thr His Ile Ser Tyr Met Pro Thr  
 290 295 300  
 Ile Lys Glu Gly Asn Ser Arg Glu Leu Met Gly Gln Gln Ser Met Pro  
 305 310 315 320  
 Asn Arg Pro Asn Tyr Ile Ala Phe Arg Asp Asn Phe Ile Gly Leu Met  
 325 330 335  
 Tyr Tyr Asn Ser Thr Gly Asn Met Gly Val Leu Ala Gly Gln Ala Ser  
 340 345 350  
 Gln Leu Asn Ala Val Val Asp Leu Gln Asp Arg Asn Thr Glu Leu Ser  
 355 360 365  
 Tyr Gln Leu Leu Leu Asp Ser Ile Gly Asp Arg Thr Arg Tyr Phe Ser  
 370 375 380  
 Met Trp Asn Gln Ala Val Asp Ser Tyr Asp Pro Asp Val Arg Ile Ile  
 385 390 395 400  
 Glu Asn His Gly Thr Glu Asp Glu Leu Pro Asn Tyr Cys Phe Pro Leu  
 405 410 415  
 Gly Gly Val Ile Asn Thr Glu Thr Leu Thr Lys Val Lys Pro Lys Thr  
 420 425 430  
 Gly Gln Glu Asn Gly Trp Glu Lys Asp Ala Thr Glu Phe Ser Asp Lys  
 435 440 445  
 Asn Glu Ile Arg Val Gly Asn Asn Phe Ala Met Glu Ile Asn Leu Asn  
 450 455 460  
 Ala Asn Leu Trp Arg Asn Phe Leu Tyr Ser Asn Ile Ala Leu Tyr Leu  
 465 470 475 480  
 Pro Asp Lys Leu Lys Tyr Ser Pro Ser Asn Val Lys Ile Ser Asp Asn  
 485 490 495  
 Pro Asn Thr Tyr Asp Tyr Met Asn Lys Arg Val Val Ala Pro Gly Leu  
 500 505 510  
 Val Asp Cys Tyr Ile Asn Leu Gly Ala Arg Trp Ser Leu Asp Tyr Met  
 515 520 525  
 Asp Asn Val Asn Pro Phe Asn His His Arg Asn Ala Gly Leu Arg Tyr  
 530 535 540  
 Arg Ser Met Leu Leu Gly Asn Gly Arg Tyr Val Pro Phe His Ile Gln  
 545 550 555 560

Val	Pro	Gln	Lys	Phe 565	Phe	Ala	Ile	Lys	Asn 570	Leu	Leu	Leu	Leu	Pro	Gly 575
Ser	Tyr	Thr	Tyr 580	Glu	Trp	Asn	Phe	Arg 585	Lys	Asp	Val	Asn	Met 590	Val	Leu
Gln	Ser	Ser 595	Leu	Gly	Asn	Asp	Leu 600	Arg	Val	Asp	Gly	Ala 605	Ser	Ile	Lys
Phe	Asp 610	Ser	Ile	Cys	Leu	Tyr 615	Ala	Thr	Phe	Phe	Pro 620	Met	Ala	His	Asn
Thr 625	Ala	Ser	Thr	Leu	Glu 630	Ala	Met	Leu	Arg	Asn 635	Asp	Thr	Asn	Asp	Gln 640
Ser	Phe	Asn	Asp	Tyr 645	Leu	Ser	Ala	Ala	Asn 650	Met	Leu	Tyr	Pro	Ile	Pro
Ala	Asn	Ala	Thr 660	Asn	Val	Pro	Ile	Ser 665	Ile	Pro	Ser	Arg	Asn 670	Trp	Ala
Ala	Phe	Arg 675	Gly	Trp	Ala	Phe	Thr 680	Arg	Leu	Lys	Thr	Lys 685	Glu	Thr	Pro
Ser	Leu 690	Gly	Ser	Gly	Tyr	Asp 695	Pro	Tyr	Tyr	Thr	Tyr 700	Ser	Gly	Ser	Ile
Pro 705	Tyr	Leu	Asp	Gly	Thr 710	Phe	Tyr	Leu	Asn	His 715	Thr	Phe	Lys	Lys	Val 720
Ala	Ile	Thr	Phe	Asp 725	Ser	Ser	Val	Ser	Trp 730	Pro	Gly	Asn	Asp	Arg 735	Leu
Leu	Thr	Pro	Asn 740	Glu	Phe	Glu	Ile	Lys 745	Arg	Ser	Val	Asp	Gly 750	Glu	Gly
Tyr	Asn	Val 755	Ala	Gln	Cys	Asn	Met 760	Thr	Lys	Asp	Trp	Phe 765	Leu	Val	Gln
Met	Leu 770	Ala	Asn	Tyr	Asn	Ile 775	Gly	Tyr	Gln	Gly	Phe 780	Tyr	Ile	Pro	Glu
Ser 785	Tyr	Lys	Asp	Arg	Met 790	Tyr	Ser	Phe	Phe	Arg 795	Asn	Phe	Gln	Pro	Met 800
Ser	Arg	Gln	Val	Val 805	Asp	Asp	Thr	Lys	Tyr 810	Lys	Asp	Tyr	Gln	Gln	Val
Gly	Ile	Leu	His 820	Gln	His	Asn	Asn	Ser 825	Gly	Phe	Val	Gly	Tyr 830	Leu	Ala
Pro	Thr	Met 835	Arg	Glu	Gly	Gln	Ala 840	Tyr	Pro	Ala	Asn	Phe 845	Pro	Tyr	Pro
Leu	Ile 850	Gly	Lys	Thr	Ala	Val 855	Asp	Ser	Ile	Thr	Gln 860	Lys	Lys	Phe	Leu
Cys 865	Asp	Arg	Thr	Leu	Trp 870	Arg	Ile	Pro	Phe	Ser 875	Ser	Asn	Phe	Met	Ser 880
Met	Gly	Ala	Leu	Thr 885	Asp	Leu	Gly	Gln	Asn 890	Leu	Leu	Tyr	Ala	Asn	Ser 895

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Ala His Ala Leu Asp Met Thr Phe Glu Val Asp Pro Met Asp Glu Pro  
                   900                                  905                                  910

Thr Leu Leu Tyr Val Leu Phe Glu Val Phe Asp Val Val Arg Val His  
                   915                                  920                                  925

Arg Pro His Arg Gly Val Ile Glu Thr Val Tyr Leu Arg Thr Pro Phe  
           930                                  935                                  940

Ser Ala Gly Asn Ala Gln His  
   945                                  950

## (2) INFORMATION FOR SEQ ID NO:55:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 98 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: double  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

GAA CTC GGA GGT GGA GGT GGA ACT AGT TTT GGA CGC GGA GAC ATT CGC  
 Glu Leu Gly Gly Gly Gly Gly Thr Ser Phe Gly Arg Gly Asp Ile Arg  
   1                                  5                                  10                                  15

48

AAT TAAAGTACTG GATTCATGAC TCTAGACTTA ATTAAGGATC CAATAAA  
 Asn

98

## (2) INFORMATION FOR SEQ ID NO:56:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 17 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

Glu Leu Gly Gly Gly Gly Gly Thr Ser Phe Gly Arg Gly Asp Ile Arg  
   1                                  5                                  10                                  15

Asn

**WHAT IS CLAIMED IS:**

1. A chimeric adenovirus coat protein comprising a nonnative amino acid sequence, wherein said chimeric adenovirus coat protein has a decreased ability or inability to be recognized by a neutralizing antibody directed against the wild-type adenovirus coat protein.
2. The chimeric adenovirus coat protein of claim 1, wherein said nonnative amino acid sequence comprises a deletion, insertion, or a replacement of a region of from about 1 to about 750 amino acids of said wild-type adenovirus coat protein.
3. The chimeric adenovirus coat protein of claim 1 or 2, wherein said nonnative amino acid sequence comprises a plurality of deletions, insertions, and/or replacements.
4. The chimeric adenovirus coat protein of any of claims 1-3, wherein said coat protein is a chimeric adenovirus hexon protein.
5. The chimeric adenovirus coat protein of claim 4, wherein said region deleted or replaced comprises a hypervariable region in either the 11 loop or the 12 loop.
6. The chimeric adenovirus coat protein of claim 5, wherein said hypervariable region is selected from the group consisting of HVR1, HVR2, HVR3, HVR4, HVR5, HVR6, and HVR7.
7. The chimeric adenovirus coat protein of any of claims 1-6, comprising a sequence selected from the group consisting of SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID

NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:44, SEQ ID NO:46, and SEQ ID NO:48.

8. The chimeric adenovirus coat protein of any of claims 1-7, wherein said nonnative amino acid sequence comprises a spacer of about 1 to about 750 amino acids.

9. The chimeric coat adenovirus coat protein of claim 8, wherein said spacer comprises the sequence of SEQ ID NO:50.

10. The chimeric adenovirus coat protein of any of claims 1-9, comprising an amino acid sequence of a coat protein of another serotype of adenovirus.

11. The chimeric adenovirus coat protein of claim 10, wherein said coat protein of another serotype is a hexon protein.

12. An isolated or purified nucleic acid that encodes the chimeric adenovirus coat protein of any of claims 1-11.

13. The isolated or purified nucleic acid of claim 12 comprising a sequence selected from the group consisting of SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:41, SEQ ID NO:43, SEQ ID NO:45, and SEQ ID NO:47.

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14. The isolated or purified nucleic acid of claim 12 or 13 comprising SEQ ID NO:49.

15. An adenoviral vector that comprises the chimeric adenovirus coat protein of any of claims 1-11.

16. A method of genetically modifying a cell which comprises contacting said cell with the adenoviral vector of claim 15.

17. A host cell that comprises the chimeric adenovirus coat protein of any of claims 1-11.

18. A method of constructing an adenoviral vector that has a decreased ability or inability to be recognized by a neutralizing antibody directed against wild-type adenovirus coat protein, which method comprises obtaining an adenoviral vector comprising a wild-type adenovirus coat protein and replacing said wild-type adenovirus coat protein with the chimeric adenovirus coat protein of any of claims 1-11.

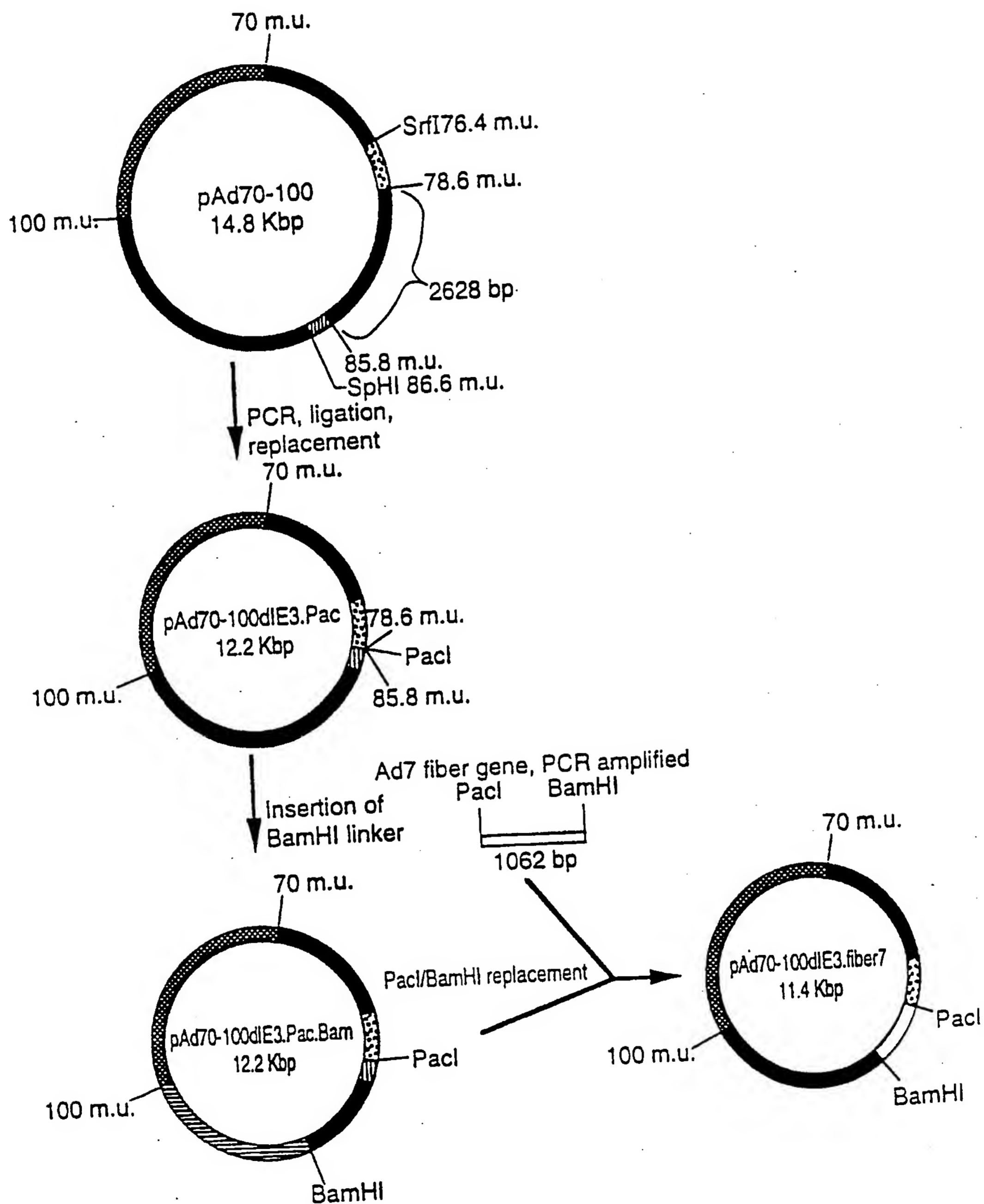


FIG. 1

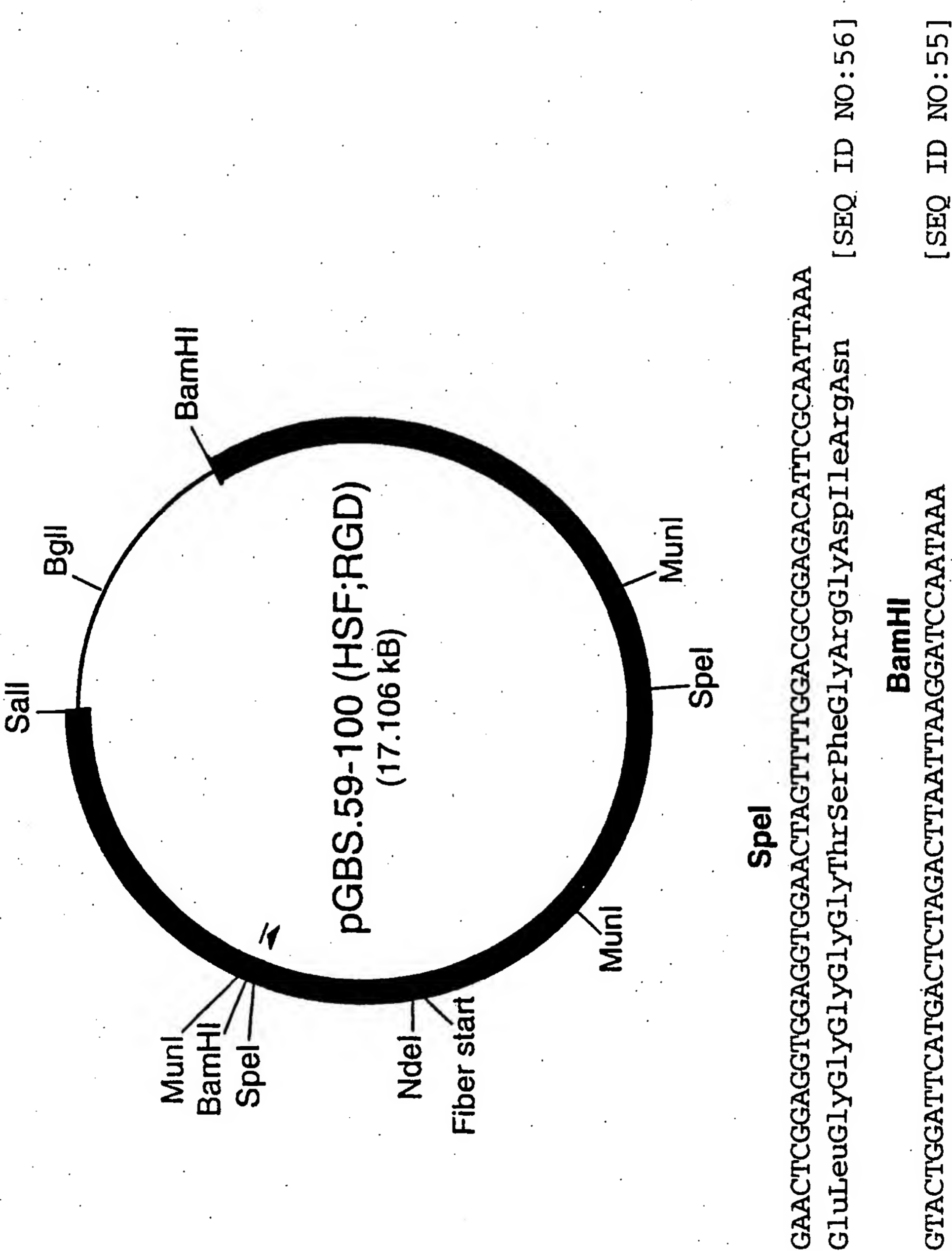


FIG. 2

# INTERNATIONAL SEARCH REPORT

Int .tional Application No  
PCT/US 98/05033

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 C12N15/86 C07K14/075 C12N15/34 C12N5/10

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 26281 A (GENVEC, INC.) 29 August 1996 see page 5, line 7 - line 23 see page 6, line 30 - line 37 ---	1-18
A	CROMPTON J ET AL.: "Expression of a foreign epitope on the surface of the adenovirus hexon" JOURNAL OF GENERAL VIROLOGY, vol. 75, no. 1, January 1994, READING GB, pages 133-139, XP002071015 cited in the application see table 1 --- -/--	1-18

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

9 July 1998

Date of mailing of the international search report

27/07/1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Cupido, M

# INTERNATIONAL SEARCH REPORT

In. tional Application No  
PCT/US 98/05033

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>CRAWFORD-MIKSZA L AND SCHNURR P: "Analysis of 15 adenovirus hexon proteins reveal the location and structure of seven hypervariable regions containing serotype-specific residues" JOURNAL OF VIROLOGY, vol. 70, no. 3, March 1996, AMERICAN SOCIETY FOR MICROBIOLOGY US, pages 1836-1844, XP002071016 cited in the application</p> <p style="text-align: center;">---</p>	1-18
A	<p>MASTRANGELI A ET AL.: "Sero-switch" Adenovirus-mediated in vivo gene transfer: Circumvention of anti-adenovirus humoral immune defenses against repeat adenovirus vector administration by changing the adenovirus serotype" HUMAN GENE THERAPY, vol. 7, no. 1, 1 January 1996, pages 79-87, XP000653452 cited in the application</p> <p style="text-align: center;">-----</p>	1-18

# INTERNATIONAL SEARCH REPORT

Information on patent family members

In tional Application No

PCT/US 98/05033

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9626281 A	29-08-1996	US 5770442 A	23-06-1998
		AU 4980496 A	11-09-1996
		CA 2213343 A	29-08-1996
		EP 0811069 A	10-12-1997